American Heart Journal

VOL. 38 AUGUST, 1949 NO. 2

Original Communications

ON CERTAIN ASPECTS OF THE NATURE AND TREATMENT OF OLIGEMIC SHOCK*

IRVINE H. PAGE, M.D.

CLEVELAND, OHIO

GEORGE BROWN was the friend of us all. It is proper that as we grow older in the science of medicine we should constantly freshen the remembrance of those who preceded us in the making of that science. George Brown was one to be remembered. Were he here he would cast a wry smile at my floundering in an already confused field. But it was just such things he liked to do.

So with another wry smile, let us consider some limited aspects of shock, with some simplifying, and, I hope, clarifying dogmatism, as I think Brown himself would have enjoyed doing.

Over the past nine years, I have followed the literature on shock and I have read a majority of the older papers. I have come away with three definite impressions: (1) The search for the initiating mechanism of oligemic shock is probably ended after many false starts. (2) Until recently, the field has been lacking in painstaking work verifying or rejecting many brilliant suggestions concerned with the mechanism of shock. (3) Most investigators have concentrated on the role of one organ or system, to the implied exclusion of others.

The nervous system, the adrenal glands, the heart, the liver: all have had their day, to be supplanted after a barely decent interval by another organ or system. But on one fact all investigators are agreed: shock represents all-embracing dissolution. Therefore, its over-all effects can probably best be measured by a quotient representing cardiac output and oxygen consumption as a measure of effective blood flow. Gesell,[1] it seems to me, has most nearly approached this concept within his "nutrient flow." He assumes that in shock, transport of nutrient material and carrying away of waste are interfered with,

From the Research Division of the Cleveland Clinic Foundation.

*The George Brown Memorial Lecture. Read at the Twenty-first Annual Scientific Meeting of The American Heart Association, Chicago, Ill., June 18-19, 1948.

either by dilution of the blood or by reduction of flow. Since the effective blood flow is seriously reduced for prolonged periods of time, it is not surprising that widespread damage occurs. Whether the lack of one specific element, such as oxygen, is chiefly at fault, or whether many substances are involved, is not known. For reasons such as these, it is probably unwise to continue the exclusive use of the terms anoxia or hypoxia to explain the cause of the tissue changes. Whatever the mechanism, widespread tissue ischemia of sufficient persistence results in shock. I must add one other impression from the literature: Carl Wiggers in his several reviews beginning in 1903 has maintained, perhaps as much as anyone, that judicial balance representative of the best in the trained scientific mind.

Let me illustrate from one of our patients how our own interest in these problems was aroused. This example also shows that blood pressure may be excessively low, but so long as no tissue ischemia occurs, shock does not appear.[2] This unfortunate patient had taken 15 Gm. of arsenic trioxide with suicidal intent. Three hours later his arterial pressure was 65/35, and twelve hours later, 45/0, and his pulse was 98 beats per minute. Curiously, while he was on the stretcher his mind was relatively clear despite the low pressure; and, importantly, his skin was warm and well perfused. Measurement showed that cardiac output had doubled while the calculated peripheral resistance remained very low. Thus, he overcame the handicap of low arterial pressure by increasing the volume output of the heart and decreasing peripheral resistance, and so avoided ischemia of the tissues and shock. Within twenty-four hours, his blood pressure had returned to normal.

It is instructive to examine the results of basal blood flow measurements in tissues, in relationship to blood pressure. Gesell gives a good example from studies in the submaxillary gland (Fig. 1).

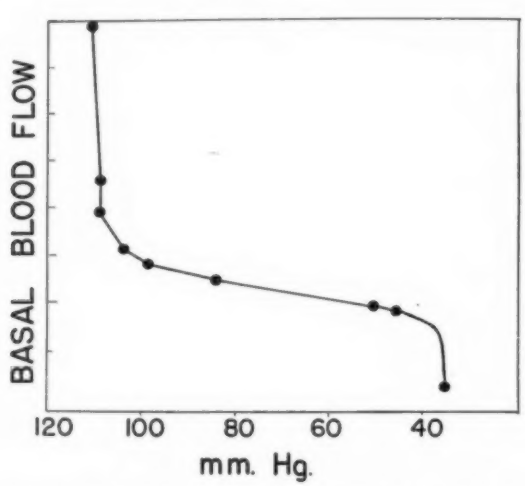


Fig. 1.—Relationship of basal blood flow to arterial pressure in the submaxillary gland. The marked fall in blood flow early and late is especially to be noted. (From Gesell, A.: Am. J. Physiol. 47:438, 1918-1919.[1])

As the first 10 to 20 mm. fall in blood pressure takes place, a profound reduction of organ blood flow occurs, at least in such nonessential organs as the submaxillary glands. The curve of fall then remains almost level during the next fall of 50 mm. and again falls off sharply at 40 mm. mean pressure. Perhaps the most dangerous of these periods is the first, because blood pressure appears to be "well maintained," yet tissue perfusion has fallen off sharply. All observers recognize the danger of arterial pressures below 50 mm. Hg and will attempt their elevation, but not so with the lesser degrees of hypotension. This relationship of blood pressure and blood flow has been formalized in the highly significant work of Norman Freeman, which will be discussed later.

It has taken possibly thirty years to recognize fully the importance of oligemia as a cause of shock. As with so many important discoveries, many investigators have contributed, and years have been required for final acceptance of their findings. Clinicians probably realized its importance first, but did nothing about it except attempt to measure it by the uncertain hemoglobin or hematocrit methods. Henderson, Robertson, and Bock[53] and Keith[54] were the first to measure the decrease by dye dilution methods. Subsequently much critical work has been performed. Of especial importance have been Blalock's[3] and Phemister's[4] demonstrations that loss of plasma at the site of injury often is sufficient to cause shock. Most investigators would now agree that this is not the only factor in the production of shock, but is certainly of prime importance. During World War II, Gregersen[5] and Gibson[6] did much to add more accurate quantitative data to this aspect of the problem. Another vital demonstration was that in shock cardiac output is low. It is difficult to ascertain precisely when this concept originated. Certainly, many had believed it for some time. By 1923, Cannon could say in his monumental book on shock, "This theory starts with the now well-known fact that the low blood pressure in shock is due to the small amount of blood pumped out by the heart." Since that time, many investigators have confirmed this finding in animals. Cournand, Richards, and their associates[7] extended the observation to man by use of the modern cardiac catheterization technique.

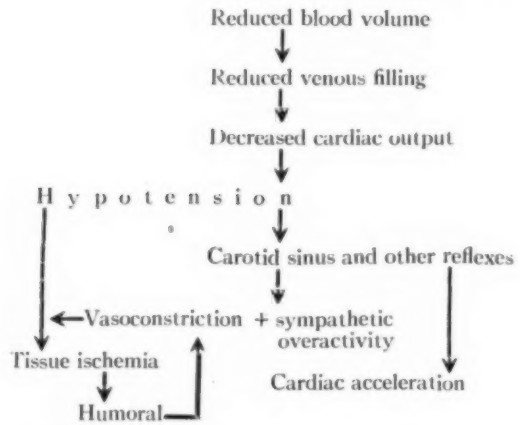
These observations, along with low blood pressure, give the picture of the state of affairs early in shock. The oligemia may be given primacy; the rest follows. (Table I.) Then begins the period of generalized dissolution in which so many chemical reaction paths are disturbed as to leave the investigator both baffled and frustrated. One must have sympathy for the biochemists catapulted into the problem of shock during the war lest they fail in their patriotic duty. This, it seems to me, is richly reflected in the admirable review of Wilhelmi,[8] yet sympathy fails to yield a satisfying degree of clarity. Changes there are, and many of great magnitude, but they are everywhere. To separate the important from the unimportant seems beyond contemporary understanding, at least any that I have encountered.

Clearly the pleasures of fresh adventure have been enjoyed but little in the past years. While much knowledge has been refined, the concentrate, I fear, has lost some of its original essence. We are likely, as it were, to mistake one solar system for the galaxy.

The more important practical clinical aspects of oligemic shock will not be touched on, since it is the part of wisdom to leave these to those with large battle experience, such as McMichael[9] and Sharpey-Schafer[10] in England, and Henry Beecher in this country.

TABLE I. KNOWN MECHANISMS IN OLIGEMIC SHOCK

SHOCK FROM HEMORRHAGE



I shall now touch on several problems that have been of especial interest to us. The first of these is concerned with the producing of experimental oligemic shock with some degree of reproducibility. Next, the occurrence of vasoconstriction, and some of the mechanisms by which it may be produced, will be considered. There follows a brief discussion of investigations into some factors influencing survival after experimental shock, such as blocking the autonomic ganglia and changing the reactivity of the blood vessels to stimuli. Finally, treatment of late shock by intra-arterial blood transfusion is described. With this outline in mind, perhaps some slim thread of continuity will be discerned.

PRODUCTION OF EXPERIMENTAL OLIGEMIC SHOCK

I shall touch on this problem only briefly. Glasser and I[11] have studied the problem for the past three years, attempting to find a "standard" method. The best we have been able to do is to define the limitations of present methods. We employed a modification of that of Wiggers and Werle,[12] in which blood is removed until the pressure is brought to 50 mm. Hg and kept there for ninety minutes. It is then lowered to 30 and held there for forty-five minutes. The blood was taken into a reservoir arranged so that the pressure within it could be kept constant. The reservoir was suspended on springs, and a writing lever attached to record the filling weight on a kymograph (Fig. 2). It was connected to a femoral artery and the connection kept open so blood could flow in or out as the arterial pressure was greater or less than that in the reservoir.

At the end of the 135-minute period of hypotension, following the method employed for the same purpose by Kohlstaedt and Page,[13] blood was transfused intra-arterially until the pressure reached the control level. We found, just as they had, that only about one-half to two-thirds of the blood was necessary to restore the pressure to control levels.

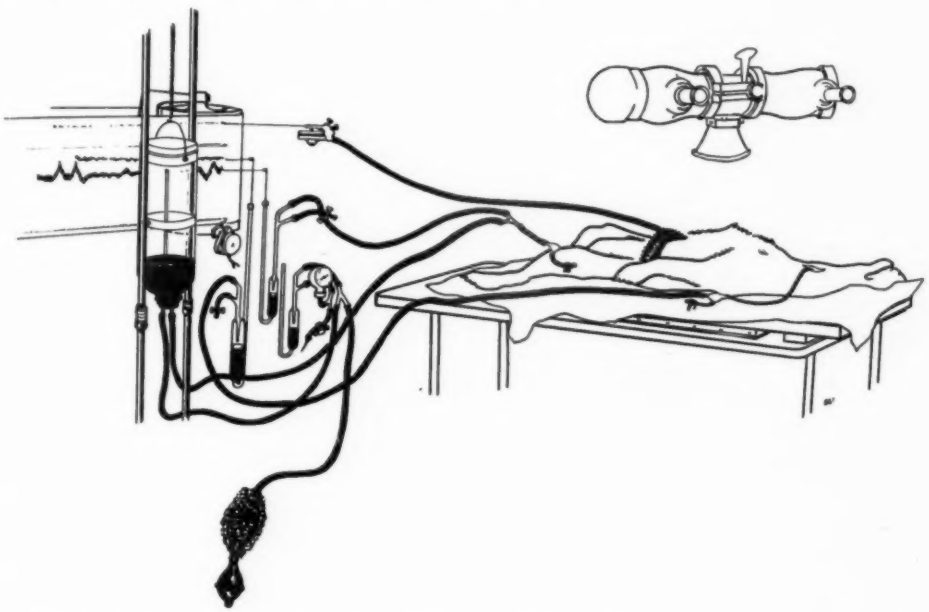


Fig. 2.—Apparatus for bleeding and arterial transfusion. The pressure reservoir is suspended on springs and its movements recorded on the kymograph by an ink-writing pen. Arterial and venous pressures and respiration are recorded.

It soon became apparent that there were wide limits within which the animals died or survived. By survival is meant unlimited survival, not survival for merely twelve or twenty-four hours. The variability was so great that we found it necessary to seek for objective criteria which would give us some clue as to whether the animals would survive or not.

Page and Kolstaedt[13,14] had employed two such criteria: (1) the return of the pressor response to angiotonin or adrenalin to its control level after retransfusion, and (2) the degree of cardiac dilatation that had occurred. We were able to confirm both, but the amount of equipment necessary for accurate measurement of cardiac size militated against its general usefulness.

The curves traced by the record of the inflow and outflow of blood from the pressure reservoir gave us a criterion of great usefulness. If during the hypotensive periods, the arterial pressure tended to fall off and blood to flow back into the animal (Figs. 3 and 4), it could be shown that prognosis was poor. Further, if all the blood removed was required to restore the level of arterial pressure to its control level, prognosis was also poor. Thus, the re-

sponse to adrenalin, the continued uptake of blood by the animal, especially during the drastic hypotensive period, and the amount of blood required by arterial transfusion to restore the control pressure, when considered together, provided criteria of significant accuracy.

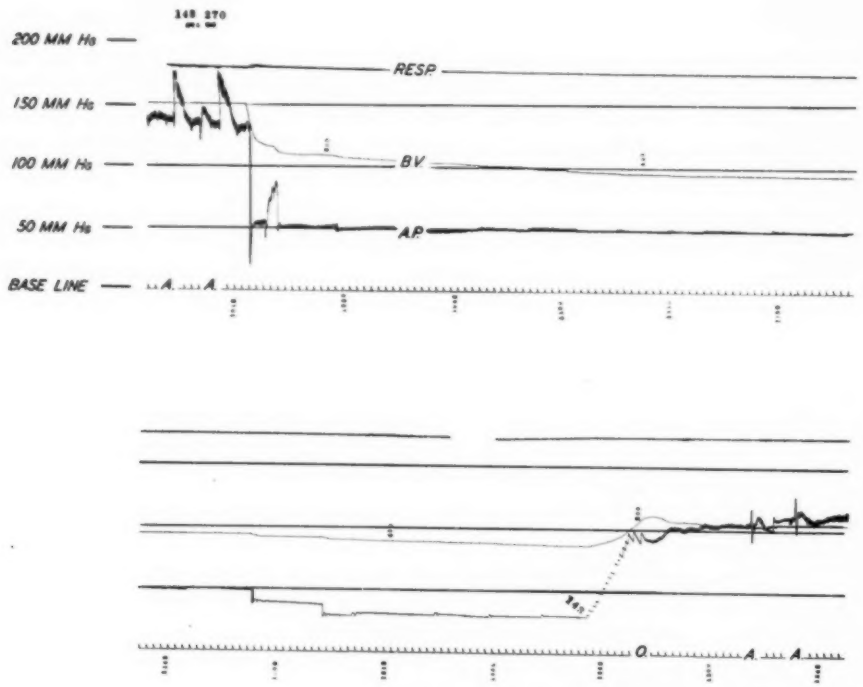


Fig. 3.—Record of dog with good prognosis after hemorrhage. Reading from above down (1) respiration, (2) weight of blood in reservoir, (3) arterial pressure, (4) time in minutes. *A* signifies adrenalin injection; *0* signifies ouabain injection. Note the lack of intake of blood during hypotensive period of 143 minutes, the small uptake to restore arterial pressure to control levels, and the return of adrenalin responsiveness.

During the first year of the work, survival among the dogs with poor prognosis was only 7 per cent, and among those with good prognosis, 35 per cent. This was well after the time that simple technical inadequacies had made themselves felt. Everyone recognizes that after the first dozen or so experiments technique has usually improved sufficiently to increase the percentage of survival, but the circumstances were different in our experiments. For no apparent reason, sometime early in the second year of experimentation a great many more animals fell into the group with good rather than poor prognosis. At that time 84 per cent of the animals had a good prognosis and correspondingly fewer had a poor one. This ratio was maintained to the end of the experiments, with, however, several weeks, and often months, of notable exceptions. During these periods, without warning a large percentage of the control dogs failed to survive and the percentage of survival returned to that of the first year (Fig. 5). We have investigated a variety of possible causative

factors in the hope that some clue to this most remarkable behavior might be found. But we have failed to find one. The importance of the phenomenon lies in the fact that survival can be so profoundly influenced by factors entirely outside our control. When the number of animals with good prognosis

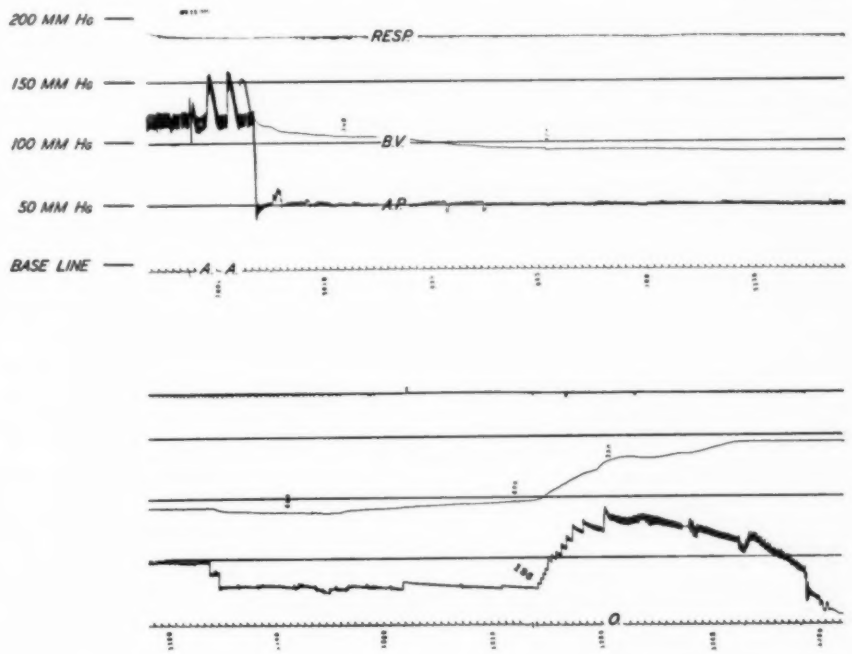


Fig. 4.—Record of dog with poor prognosis after hemorrhage. Symbols as in Fig. 3. Note the intake of blood during the latter part of the hypotensive period, large intake to restore blood pressure to control level, and poor return of response to adrenalin.

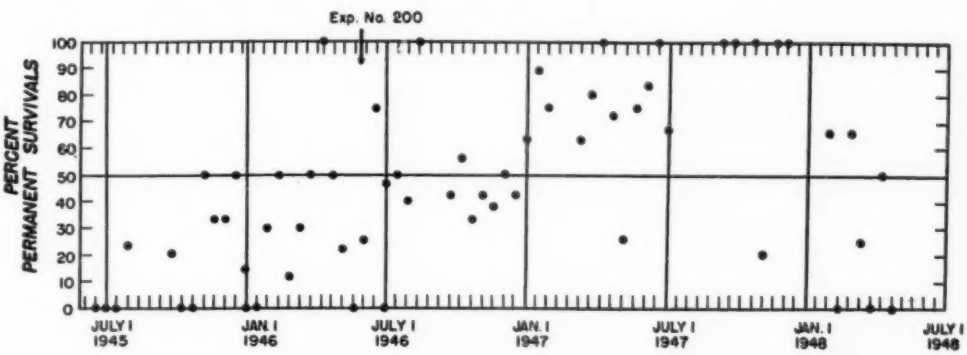


Fig. 5.—Percentages of permanent survival after shock procedure for two-week periods from July, 1945, to June, 1948. No division is made between those with good or poor prognosis. (From Glasser, O., and Page, I. H.: Am. J. Physiol. **154**:297, 1948.[11])

rises from 35 to 84, it is evident that something in the mechanism has eluded us and that this something is of the greatest importance. The second reason that the recognition of the phenomenon is important is that in serial experiments

where uniformity of behavior is expected, it may not occur. Animals with good prognosis cannot fairly be compared with those of poor prognosis. This distinction seems of real importance. Thus, the hope that there is such a thing as regularly reproducible "standardized" shock seems to be only statistically true, and then only when a sufficient number of experiments have been performed over a long enough period. We have studied the shock procedure in 482 dogs to obtain this information. This may seem a great many for such uninspired knowledge, yet it seems to me to pose one of the fundamental problems in the field of shock.

VASOCONSTRICTION IN SHOCK

The problem of vasoconstriction in shock, viewed superficially, seems relatively simple. But closer analysis reveals extraordinary complexity, and despite much good work, there is still no satisfying answer. I shall deliberately avoid the problem of the relationship of vasoconstriction to peripheral resistance, thereby freeing myself of a great and controversial burden. It is a problem that the masters of hemodynamics such as Wiggers, Visscher, and Hamilton refuse to answer categorically.

What, then, are the caliber changes in the small and smallest vessels in various parts of the vascular tree during the different stages of shock? Probably depending on the method of examination, the published results indicate vasodilatation in some investigations and vasoconstriction in others. Where tissues were manipulated and exposed, or the natural blood supply altered by transfusion, vasodilatation was usually observed. When these were avoided, vasoconstriction seemed to occur. I shall not trouble you with a recitation of the many important contributions to this problem, but rather take the speaker's prerogative of presenting the work in which he has participated.

Dr. Richard Abell and I[15-17] employed the elegant method of Clark and Zintel, in which the exteriorized gut and its mesentery are placed in an observation chamber sewn into the belly wall. This allowed the tissues to be examined at any time with little disturbance to the animal. Cats, dogs, and rabbits were studied under pentobarbital anesthesia after tourniquet, burn, and hemorrhage.

The following course of events was observed (Fig. 6). Marked constriction of the arteries and arterioles occurred usually within an hour after, for example, incomplete occlusion of the limbs, lasted several hours, and finally gave way to relaxation an hour or more before death. The constriction was associated with reduced blood supply to the mesentery and intestine, and with reduced venous return from them. The veins of the mesentery also became constricted, but showed less tendency to dilate as death approached. The lymphatics were likewise narrowed. With severe hemorrhage, the same effects were observed, but the vasoconstriction occurred more promptly. The vasoconstriction after hot water burns also was very severe, and, as after the other shocking procedures, preceded by some time the fall in arterial pressure. The

closing of arteriovenous anastomoses further reduced the return of blood to the right heart but aided the capillary circulation.

There seems to be little disagreement that the vessels of the limbs are constricted. This is particularly striking in patients, and led Freeman to the correct clinical view that simple observation and palpation of the extremities is usually the most useful sign of shock. Recent work of Wiggers, Opdyke, and Johnson[18] leaves little doubt that resistance to blood flow is increased in the liver, a highly important vascular bed, especially in the dog because of its somewhat unique valvular arrangement. The increase in resistance may well account for the intestinal bleeding so commonly seen in dogs after shock, but rare in human beings. The spleen is also the source of some increase in resistance. Mesenteric resistance also increases during hemorrhagic hypotension (Selkurt, Alexander, and Patterson[19]). The only important area so far studied in which resistance decreases rather than increases is the coronary circulation, according to Opdyke and Foreman.[20] During hemorrhagic hypotension, coronary flow decreased to 30 to 60 per cent of the control flow, and flow resistance was greatly decreased. Following reinfusion of all of the withdrawn blood, coronary flow increased 121 to 420 per cent of the control. Vasodilatation appeared to play a prominent part in the decrease in resistance.

Vasoconstriction in the kidneys is of very especial interest to Corcoran and myself and will therefore be reviewed in somewhat more detail than the other vascular beds. There is a very practical reason for doing this, as well. Treatment of shock has so much improved that a not inconsiderable number of patients are kept alive long enough to die of the renal effects of shock rather than of the shock itself. The work I shall now report is chiefly due to Corcoran; started in 1939, it was later carried on under contract with the Office of Scientific Research and Development.

SHOCK AND THE CRUSH SYNDROME

When one organ receives almost one-fourth of the total cardiac output, it is not difficult to understand why this interests greatly those concerned with the problem of shock. The kidneys receive just about this amount.

The renal blood flow decreases sharply after hemorrhage, with a disproportionate decrease in glomerular filtration in dogs (Corcoran and Page,[21] Phillips, Dole, Hamilton, Emerson, Archibald, and Van Slyke,[22] Selkurt[23]), and in human beings (Lauson, Bradley, and Cournand[24]). Repeated prolonged hemorrhage decreases the ability of the kidneys to respond to transfusion by restoration of control blood flow and filtration rate (Fig. 7). The explanation of this vasoconstriction, so intense, early, and persistent, seems to be partly humoral and partly nervous. Which is the more important, we are at present unable to say. That the decrease in blood flow is not due to decrease in arterial pressure alone is shown by the observation[25] that reduction of blood flow during the onset of shock due to partially occluding tourniquets occurs well before pressure falls, as will be seen in Fig. 8.

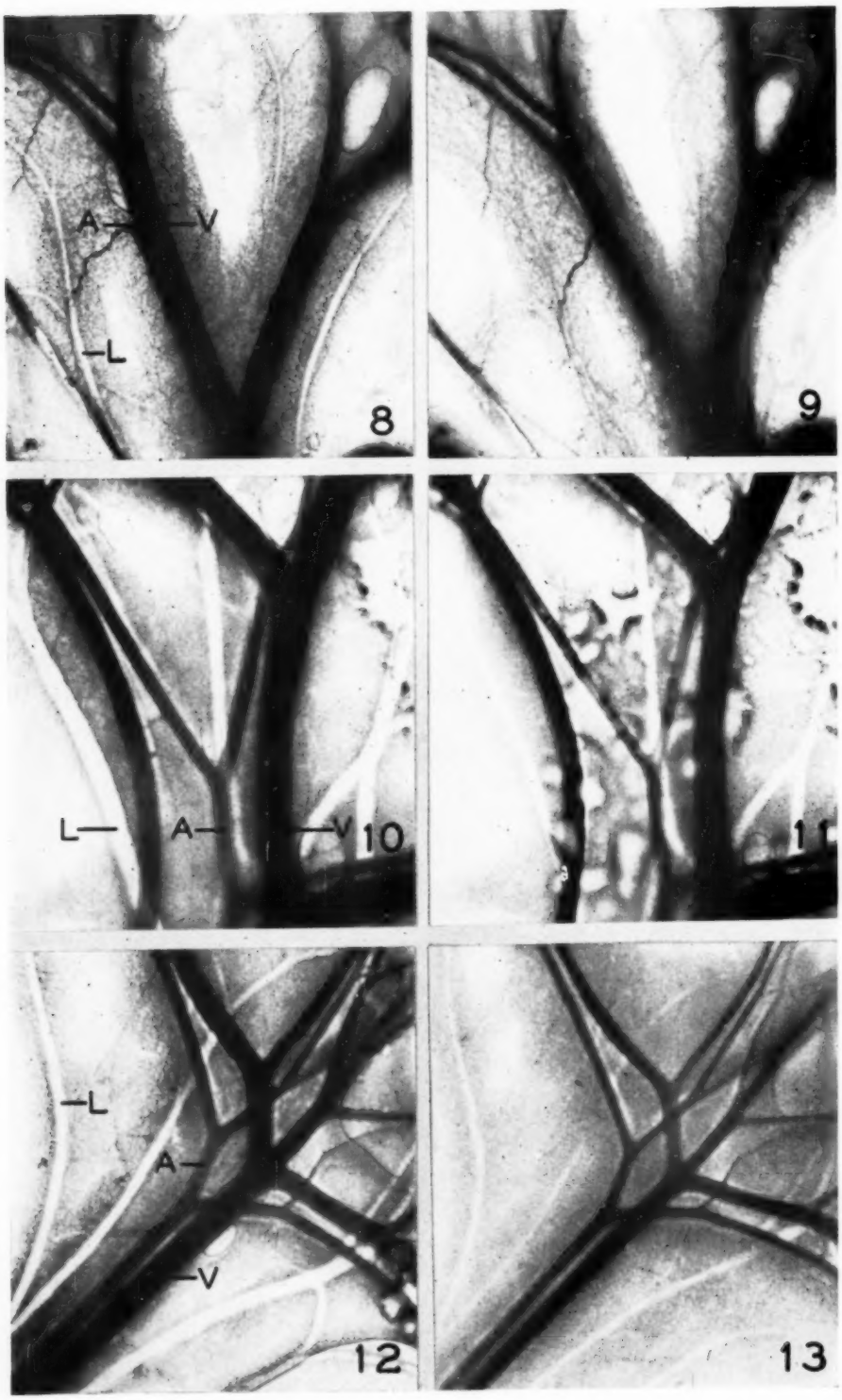


Fig. 6—*See opposite page for legends.*

You will all recall that the term crush syndrome became common during World War II. Actually, the crush syndrome had been seen and described during World War I. But Bywaters and Beall,[26] in 1941, were the first to investi-

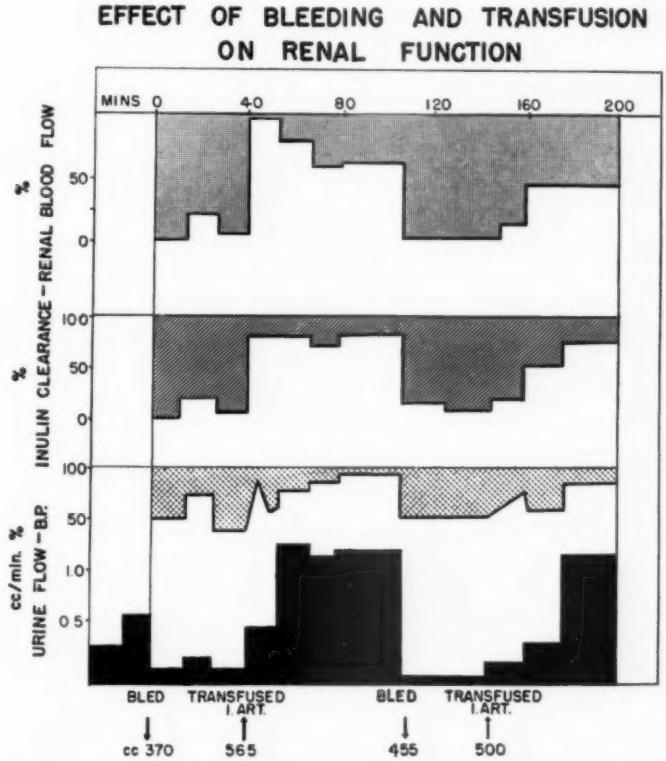


Fig. 7.—The effect of bleeding and arterial transfusion on renal blood flow, glomerular filtration, blood pressure, and urine flow. After the second bleeding, the persistent ischemia of the kidneys is evident.

Fig. 6.—Photographs of blood and lymphatic vessels in intestinal-mesentery chambers in anesthetized cats.

8, Control photograph of vessels in a portion of the mesentery of an adrenalectomized cat (Cat 11). Both adrenal glands had been removed three hours and twenty minutes before. This photograph was taken at 2:20 P.M. The pressure at this time was 136 mm. Hg (× 3.6).

9, The same vessels shown in *8*, at 3:37 P.M. Pressure 70 mm. of mercury. The cords were tied on the legs at 3:12 P.M. The arteries are constricted and the veins and lymphatics narrowed. The cat died in shock at 9:15 P.M. (× 3.6).

10, Control photograph of vessels in a portion of the mesentery of a nephrectomized cat (Cat 9) taken at 11:29 A.M. Pressure 120 mm. of mercury. The kidneys were removed the day before this photograph was taken. *A*, artery; *V*, vein; *L*, lymphatic (× 6.3).

11, The same vessels as shown in *10*, at 3:37 P.M. Pressure 70 mm. of mercury. The cords were tied on the legs at 11:52 A.M. and were cut at 3:19 P.M. The arteries are constricted and the veins and lymphatics narrowed. The cat died in shock at 5:10 P.M. (× 6.3).

12, Control photograph of blood vessels in a portion of the chamber. This photograph was taken at 1:07 P.M. Pressure 84. mm. Hg (× 6.3).

13, The same vessels as in *12*, after 32 c.c. of blood had been drawn from the femoral vein. This photograph was taken at 3:42 P.M., and the pressure at this time was 110 mm. of mercury. The blood was drawn as follows: 10 c.c. at 1:38 P.M.; 10 c.c. at 2:15 P.M.; 12 c.c. at 3:40 P.M. The arteries are constricted and the veins and lymphatics narrowed (× 6.3).

(From Page, I. H., and Abell, R. G.: J. Exper. Med. **77**:215, 1943.[15])

gate seriously the nature of the problem. Their contributions were of major importance. As this matter became more important during the war, especially because of air raids, many others took up the investigation. I do not wish to divert your attention too long from our main thesis, the shock problem; nevertheless, it is worth viewing the renal problem of shock as an integral part of shock itself.

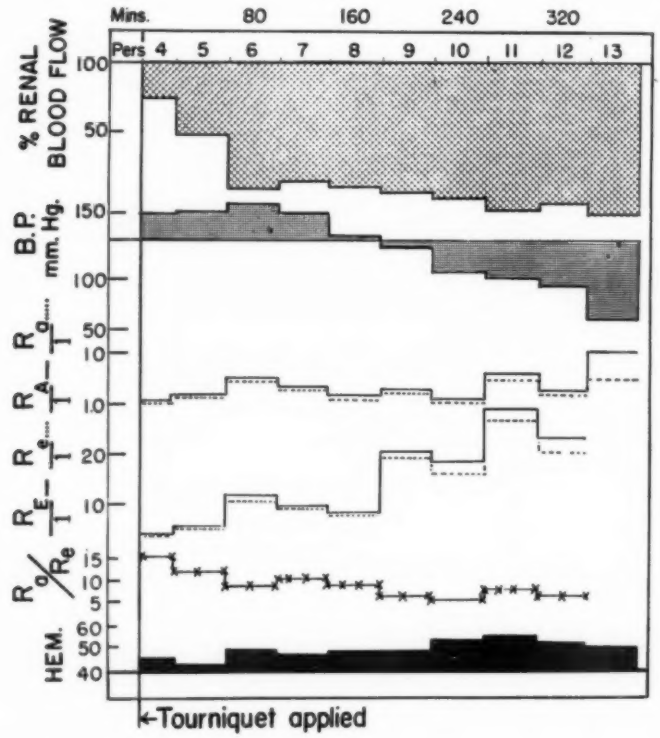


Fig. 8.—Effect of tourniquet application on total renal blood flow and blood pressure. Calculated renal resistance and hematocrit of resistance (R) are shown as ratios of the control level, which is taken as equal to 1; R_A, total afferent arteriolar resistance; R_a, the same corrected for changes of blood viscosity; R_E, total efferent arteriolar resistance; R_e, the same corrected for viscosity. The ratio R_a/R_e expresses the relative changes of arteriolar resistance proximal and distal to the glomeruli. *Hem.* = hematocrit index. (From Corcoran, A. C., Taylor, R. D., and Page, I. H.: Ann. Surg. **118**:871 1943.[25])

Corcoran and I[27,28] have reviewed the literature in some detail elsewhere, and I refer you also to some excellent review articles, covering special phases of the subject, by Macgraith,[29] Lucké,[30] Mallory,[31] and Moon.[57] Regarding the experimental investigation, suffice it to say here that we have been able to produce renal lesions in rats which leave little to be desired as reproductions of the human syndrome. It was always necessary to produce shock in the rats before injecting a solution of myoglobin to produce the lesions. Experimental crush syndrome thus seems due to coexistence of severe renal ischemia, hypotension, and myoglobinuria. The conditions of pigmentary precipitation (aciduria, oliguria) are met, while the kidneys are further damaged because of

lack of blood flow. There are doubtless many other mechanisms leading to much the same result, but a recitation of these would lead us too far afield.

Treatment obviously consists first in remedying the shock, thus re-establishing some degree of urine flow. The lessening of toxic absorption from the area of injury and of loss of plasma into it by pressure bandages, and the establishment of a rapid rate of urinary flow by administration of a diuretic, such as mannitol, constitute the three bases of treatment. It is far better, however, to avoid the syndrome by prompt treatment of the shock. In the past three years it has become increasingly apparent that crush syndrome and hemoglobinuric nephrosis are not limited to the battlefield.

MECHANISM OF THE VASOCONSTRICTION

Most of you will recall, during the last surge of interest in shock during World War I, that the vasomotor center was one of the chief points of attack. Its failure was held by some to be primary in the cause of shock. Others could demonstrate no failure at any time. To review this phase of the subject would serve no purpose, and so I shall content myself with the statement that there is no cogent evidence to suggest the primacy of failure of the vasomotor center. That it is weakened as shock deepens can hardly be doubted.

At least three possibilities suggest themselves to explain why the blood vessels constrict when blood volume is reduced: (1) physical factors, (2) active neurogenic contraction, and (3) active humoral contraction. The first of these is for the expert in physics and hemodynamics to contend with. I have no means of evaluating this concept. Good investigators take the matter seriously, and so I refer you to them.[32,58] The second is not easy to register in quantitative terms, but such experiments as there are indicate an important neurogenic element in the vasoconstriction. It was probably first shown most clearly by Seelig and Joseph[33b] when section of the nerves to a rabbit's ears caused dilatation in the strongly constricted vessels of a rabbit in shock. The explanation of their results is not as simple as it seemed thirty-three years ago; nevertheless, their demonstration carries conviction.

The third possibility, namely the humoral mechanisms, baits the investigator by its apparent simplicity. But, like the country maid, he soon learns. We first suspected the presence of a chemical vasoconstrictor when perfusing plasma, or what seemed to be plasma, of shocked dogs through a rabbit's ear perfused with calcium-free Ringer's solution of plasma.[33] Severe and prolonged constriction resulted. The vasoconstrictor was found in plasma ultrafiltrate as well as in plasma and lymph[34] (see Table II). Using a method of fatiguing the vascular muscle so as to obliterate the action of the test drug, it was possible to show that this substance had a similar action regardless of the method by which shock was produced. It did not resemble the usual vasoconstrictors, or even histamine. To our genuine surprise, it appeared in the plasma even after nephrectomy, adrenalectomy, destruction of the nervous system, or renal denervation. The amount of it seemed variable.

TABLE II. CONSTRICTION OF THE VESSELS OF A PERFUSED RABBIT'S EAR RESULTING FROM PLASMA AND ULTRAFILTRATE OF SHOCKED DOGS

	REDUCTION OF FLOW IN MINUTES	PER CENT REDUCTION OF DROP RATE
Control	½	20
Four hours after release of tourniquets	7	59
Control—bilateral nephrectomy	2½	54
Two hours after tourniquets	9	60
Control	1½	25
Two and one-half hours after severe hemorrhage	6½	48
Control	¼	16
After scalding	16	75
Ultrafiltrate of plasma after scalding	15	56
Control	1¼	34
After intestinal stripping	6½	85

We have made a much more recent effort, with Robert Taylor and John Reinhard, to learn more about vasopressors or dilators in shocked animals, by cross-transfusion experiments. Two to three days before the experiment, nephrectomy was performed in both animals. The cross transfusion can often be performed without anesthesia, but its use has seemed to make no significant difference in any case. At intervals of about fifteen minutes, test doses of 600 c.c. of blood are crossed, care being taken that the same amount of blood is in transit each way simultaneously. Blood can be transfused back and forth in nephrectomized dogs without affecting the arterial pressure of either animal. But if occluding tourniquets are placed on both hind legs of a nephrectomized donor animal for five hours, and then released, blood from such an animal shows a significant pressor action in the indicator dog, while the latter's blood causes no rise in arterial blood pressure in the donor (Fig. 9). Unfortunately, the story is seldom as simple as this because, commonly, the same type of arterial pressure rise occurs under a variety of conditions unassociated with manifest shock. It seems unlikely, therefore, that this could be the only vasoconstrictor involved in shock.

After several such crosses, no further, or much diminished, responses occur, due, we believe, to exhaustion of the vasopressor substance. If the indicator dog is given enough Dibenamine and Priscol to block the action of adrenalin, cross transfusion before exhaustion of the pressor substance in the donor dog causes marked rise in arterial pressure. But if the dosage is increased sufficiently to block nor-adrenalin, no response to cross transfusion occurs. This observation suggests strongly that the substance from the shocked animals is nor-adrenalin or sympathin-like.

The function of the renal vasopressor system, renin, renin-substrate, and angiotonin (hypertensin) in shock is not clear. Sapirstein, Ogden, and Southard[35] first reported the presence of a renin-like substance after hemorrhage. They suggested that it acted as a humoral homeostatic agent. Collins and

Hamilton[36] found that an angiotonin-like substance increased in the plasma after hemorrhage, while renin-substrate at first rose, then fell, as the hypotension was continued in both intact and adrenalectomized dogs. It is their view that renin from the animal's own kidneys exhausts the renin-substrate, so depriving the body of a compensatory mechanism.

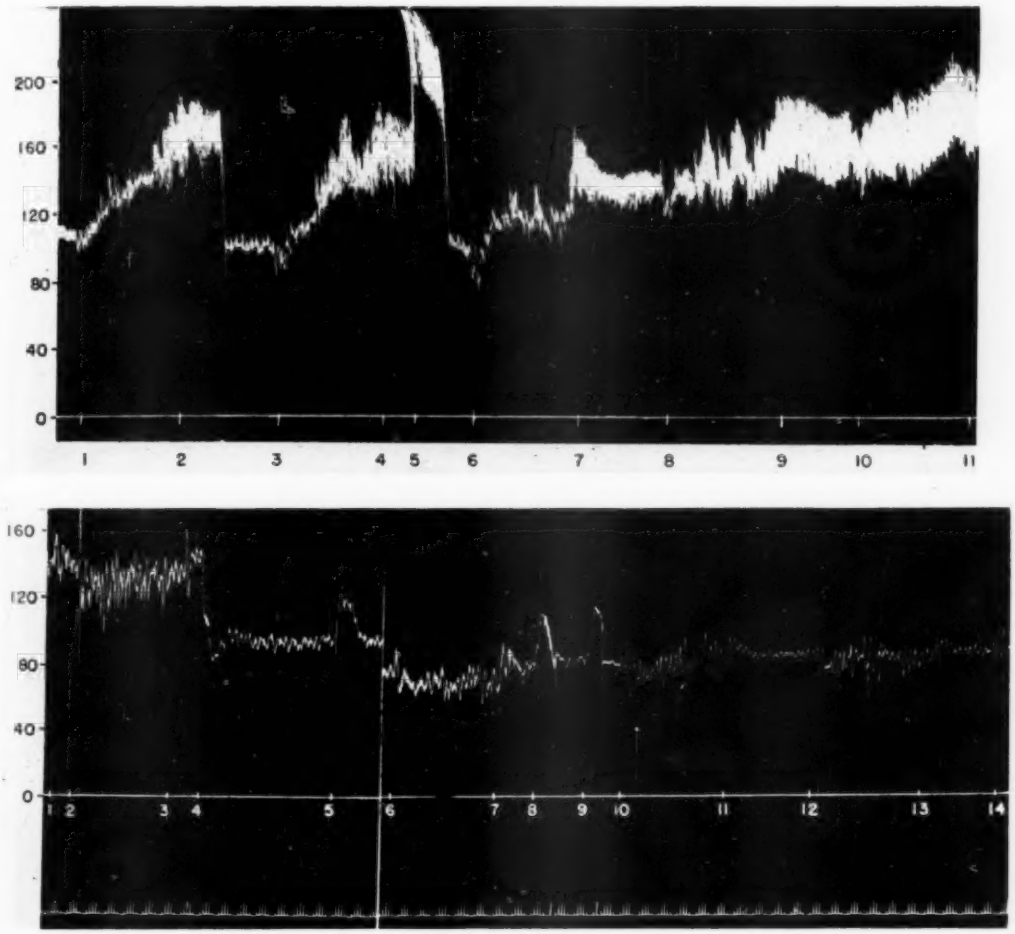


Fig. 9.—Cross transfusion of nephrectomized (two-day) tourniquet dog with a nephrectomized (two-day) dog.

Top graph: Nephrectomized dog. *1-2*, Transfusion 600 c.c.; *3-4*, same; *5*, adrenalin 0.2 c.c.-1:20,000; *6-7*, transfusion; *8-9*, same; *10-11*, same. Time, two hours. *Lower graph*: Nephrectomized tourniquet dog. *1*, Adrenalin; *2-3*, transfusion; *4*, tourniquets removed (had been on five hours); *5*, adrenalin; *6-7*, transfusion; *8-9*, adrenalin; *10-11*, transfusion; *12-13*, same; *14-15*, same.

Further and rather more complete evidence is supplied by Huidobro and Braun-Menéndez.[37] They found renin in the systemic blood of dogs after hemorrhage if the kidneys were intact. It was detected after so short a period as four to eleven minutes of profound hypotension. Normally, according to

present crude methods of assay, minimal amounts of renin are secreted by the kidneys.

While it is inferred that the renin vasopressor system is acting as a homeostatic mechanism, there is as yet no proof that this is so. The initial simplicity of the humoral system of which I spoke has vanished beneath even superficial examination!

But there is still another vasoconstrictor, and possibly the most important one of them all. As long as eighty years ago, physiologists were aware that defibrinated blood or serum did not perfuse well through isolated organs because of the vasoconstriction it caused. Somewhat later, and I shall not attempt to document the literature as we have done elsewhere,[38] it was recognized that this substance formed when blood clotted and seemed to be associated in some way with the presence of platelets.

Our interest in this factor was aroused on two scores. First, we found pressor and constrictor substances in shocked animals' blood in which the organ of origin seemed to have eluded us. Second, the vascular problem of the spread of hemorrhage in tissue, as, for example, that following infarction of the myocardium or lung, has interested us greatly. Perhaps an ancillary reason is that in assays for pressor substance in the blood of hypertensives, the possible presence of this vasoconstrictor introduced many uncertainties.

Dr. Maurice Rapport, Dr. Arda Green, and I[39] decided the only satisfying way of dealing with the problem would be the isolation and attempt to crystallize the factor to see with what we were really dealing. But it soon became apparent that the amounts present in beef, human, or pig serum, were minuscule. However, it was finally possible, by working up small batches of serum at a time, to obtain from about two tons of serum enough material to start work on purification. Success depended chiefly, I think, on the finding that from a butyl alcohol solution the active material could be precipitated by nitrobarbituric acid and on the fact that the rabbit's ear perfusion method admirably served the purpose of quantitative assay. Without this much-maligned method, the isolation would not have been possible.

The substance was finally obtained in thin, rhomboid, yellow platelets, melting at 212 to 214° C. (Fig. 10). A single analysis gave the following ratios: $C_{14} : H_{21} : O_3 : N_5 : H_2SO_4$. I shall not trouble you with the other chemical data as they are not pertinent to our discussion. We have suggested the name serotonin to indicate its source from serum and its activity in causing constriction.

Injection of an aqueous solution of this substance into dogs or cats anesthetized with pentobarbital produced a marked rise in arterial pressure, which was augmented in a chronically sympathectomized animal. The response after pithing was slightly reduced or unchanged (Fig. 11). The rabbit's ileum is sharply contracted by it. The vasoconstrictor activity of the crystalline substance in our perfused rabbit's ear preparation is more than twice that of an equal weight of adrenalin. Constriction is obtained by 0.002 microgram in the ear vessels.

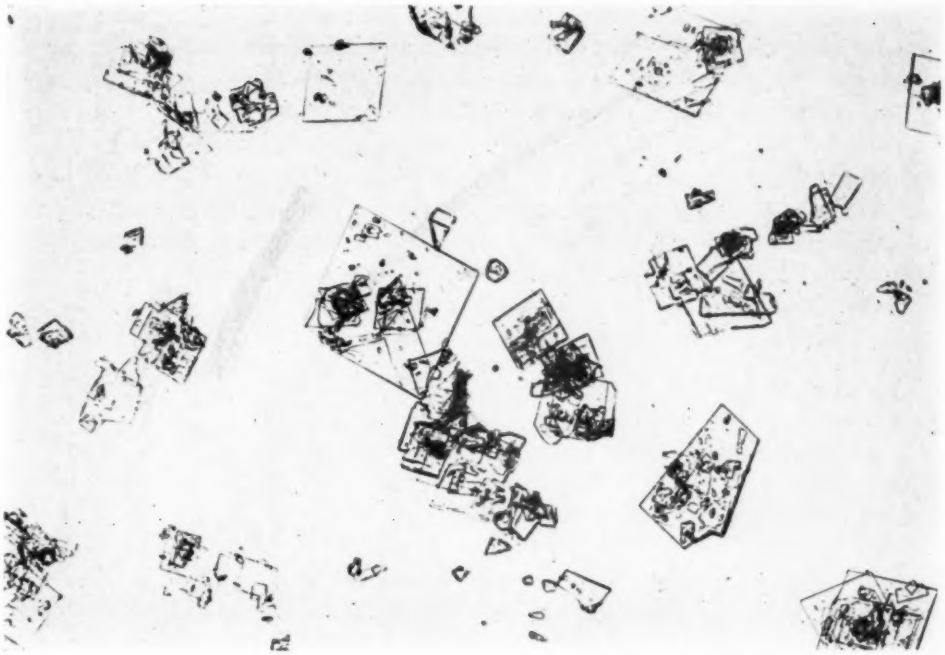


Fig. 10.—Crystals of serotonin.

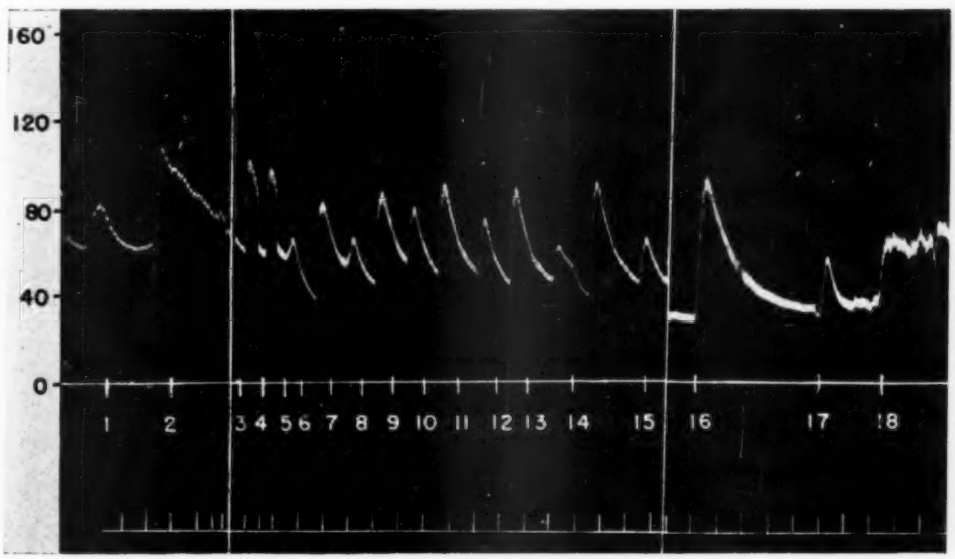


Fig. 11.—Pressor effect of serotonin and adrenalin on intact, pithed, and tetraethyl ammonium-treated, anesthetized cat (No. 472). *1*, adrenalin 0.1 c.c. 1:20,000; *2*, serotonin 0.1 c.c. 1:4,000, pithed; *3-4*, adrenalin; *5*, serotonin; *6*, adrenalin; *7*, serotonin; *8*, adrenalin; *9*, serotonin; *10*, adrenalin; *11*, serotonin; *12*, adrenalin; *13*, tetraethyl ammonium 5 mg. per kilogram; *14*, adrenalin; *15*, serotonin, four more doses of 5.0 mg. of tetraethyl ammonium; *16*, adrenalin; *17*, serotonin; *18*, renin. (From Rapport, M., Green, A. A., and Page, I. H.: Science **108**:329, 1948.[39])

Another finding of interest is that lung tissue contains an enzyme which destroys serotonin.[40] Presumably this is the mechanism by which the vasoconstrictor is removed in perfusion experiments when the blood is passed through the lungs before entering the perfused organ.

I need hardly point out that as yet we know nothing about the part, if any, played by serotonin in shock. But it is tempting to believe that, after trauma and hemorrhage, it either aids in constricting the blood vessels around clots to prevent further hemorrhage, or acts as a constrictor to keep the blood pressure up. But this is pure speculation.

FACTORS INFLUENCING SURVIVAL FROM EXPERIMENTAL SHOCK

We have found no regular correlation between survival after the shock procedure and a number of obvious environmental factors. Thus, weight of the animal, amount of blood required to lower the blood pressure, degree of hydration of the animal, season, initial hemoglobin or hematocrit, initial blood pressure, and other factors showed no significant relationship to survival of the animal.

Since there is good evidence to suggest that as shock progresses, the efficiency of the myocardium becomes impaired, as Wiggers first suggested,[41] and, I believe, as we have substantiated with further evidence,[42] it seemed of interest to study the effect of ouabain on survival. Ninety-four experiments showed that it did not alter survival, though it seemed to lessen the harmful effects of overtransfusion. The drug with real power to influence the outcome was tetraethyl ammonium chloride. Three years ago, H. C. Wiggers[43] presented preliminary evidence that treatment with Dibenamine increased the ability of dogs to withstand hemorrhagic shock. Tetraethyl ammonium ions block ganglionic transmission in all autonomic ganglia. This is followed, as Taylor and I[44] showed, by marked augmentation of the pressor-depressor responses to a wide variety of vasoactive agents.

When tetraethyl ammonium chloride was given in fifty-one experiments, either before or during the shock procedure, survival was increased in the animals with good prognosis from 85 to 96 per cent, and in those with poor prognosis, from 25 to 44 per cent.

The reason for this improvement seems to us to lie in the important observations made ten years ago by Freeman, Shaffer, Schecter, and Holling.[45] They showed that in dogs which had had total sympathectomy, blood pressure could be reduced to lower levels and for longer times without producing shock than could be done in normal dogs. But the former animals were unable to tolerate as large hemorrhages as the latter. The difference in reaction was correlated with the peripheral blood flow. In normal dogs, as the arterial pressure was reduced by hemorrhage to 70 mm. Hg, blood flow was reduced below 2.0 c.c. per minute, while in the sympathectomized animal it was above 2.0 cubic centimeters. The preferential treatment of blood supply to vital centers is lost in the sympathectomized animal, but as long as these centers receive sufficient blood supply, all the tissues of the body probably receive an adequate

amount of blood, and shock is prevented. Much the same mechanism seems to be involved in the experiments of Phemister, Eichelberger, and Lacstar,[60] in which they show that section of the spinal cord at C_8 makes the dogs more resistant to shock than equally low blood pressure elicited by hemorrhage or local fluid loss.

In experiments with Dr. John Reinhard and Dr. Otto Glasser, we found[61] that section of the cord at C_6, several days before the hemorrhage, produced a preparation not unlike the tetraethyl ammonium chloride-treated animal. Somewhat less blood needed to be removed (3.9 per cent, as compared with 5.1 per cent for normal animals) to reach the hypotensive levels, and the animals withstood the procedure with less apparent injury than normal dogs. Indeed, it was possible to subject two of the animals to a repetition of the procedure three days after the first experiment (Fig. 12). Even though only three-fourths of the blood was returned during each retransfusion, they both survived. The animals were, as was to be expected, hypersensitive to vasoactive chemical stimuli. It seems possible, if unproved, that this, along with the better perfusion of tissues, confers the heightened ability to withstand shock.

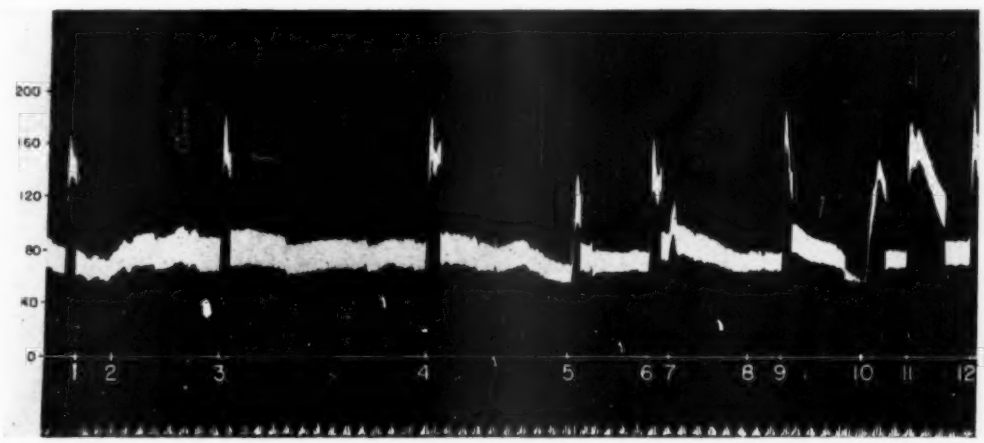


Fig. 12.—The uptake of saline from reservoir connected to the femoral artery, and adrenalin response in an unanesthetized dog (weight 7.8 kilograms) whose spinal cord had been sectioned at C_6 one day before. Fluid intake at top represents 1.0 liter. Time in minutes. Adrenalin 0.2 c.c. 1:20,000. *1*, Adrenalin; *2*, saline reservoir opened at 60 mm. Hg pressure; *3-6*, adrenalin; *7-8*, tetraethyl ammonium chloride 5 mg. per kilogram; *9-12*, adrenalin.

In view of these results, it became imperative to examine the effects of removal of other organs. Experimental results are at variance, and opinion, as well, is greatly divided as to the part the kidneys play in the mechanism of shock. Animals subjected to the shock procedure at various times after nephrectomy withstood it apparently neither better nor worse than did normal animals. We were unable to detect a difference. In some anesthesia was used and in others it was not used. The same result was obtained by Bobb[55] in nephrectomized and normal dogs subjected to compression of the hind legs

for six hours. Further, Hechter, Bergman, and Prinzmetal[56] could find no influence of the renal pressor system on either mortality or survival time in mice subjected to burn shock.

Next the liver was removed in our dogs. The animals usually were in excellent condition for periods up to ten hours or more after the operation. Most of them lost a significant amount of blood by diapedesis through the peritoneum. To our great surprise, these animals withstood the shock procedure quite as well as did normal dogs. The blood pressure curves are superimposable. As in the case of the animals with cord section, somewhat less blood is shed to produce comparable blood pressure reduction. In other experiments both the kidneys and the liver were removed, but still without change in the response to the shock procedure.

We recognize that the meaning of these experiments is difficult to determine. The fact that with the exclusion of the liver a large vascular bed is removed, along with a not inconsiderable amount of blood, may mean a change in the entire circulation. With many reservations in mind, about the most that one dare say is that it is altogether surprising that so little difference was observed in the immediate response to hemorrhage. Especially in the case of hepatectomy, the unavoidable loss of blood into the peritoneum and the removal of such a large blood-containing organ militate against the animals' ability to withstand hemorrhage, yet we detected no difference. For these and other reasons, it seems wise to record the observations, which are in sufficient number to be indisputable, but to leave interpretation for the future.

THE REACTIVITY OF BLOOD VESSELS

It is not an easy matter to decide how important are changes in the responsiveness of blood vessels to stimuli during the course of shock. We have seen that substances which affect the vasoconstrictor activity of the nerves, such as tetraethyl ammonium chloride and Dibenamine, affect survival after hemorrhage. The former increases vascular responsiveness to agents like adrenalin, while the latter decreases it. Thus, we might conclude that it makes little difference what the drug does to the reactivity of the vessels, except for the caution that the action of these drugs is exceedingly complicated. Evidence of this sort needs be accepted with wide reservation.

What, then, is the evidence favoring the view that vascular reactivity is important in shock? Six years ago we observed that the pressor response to angiotonin and adrenalin fell progressively either after injury to the central nervous system or after shock from hemorrhage or scalding (Fig. 13). In the case of hemorrhagic shock, if the response returned to full vigor after retransfusion, the likelihood of survival was materially increased.

The heart participated in the loss of responsiveness, as demonstrated by the lack of response to adrenalin when its contractions were studied in a cardiometer.[46] Not only does the blood pressure show far less rise after a dose of adrenalin, but the heart does not exhibit the usual sharp diminution in size

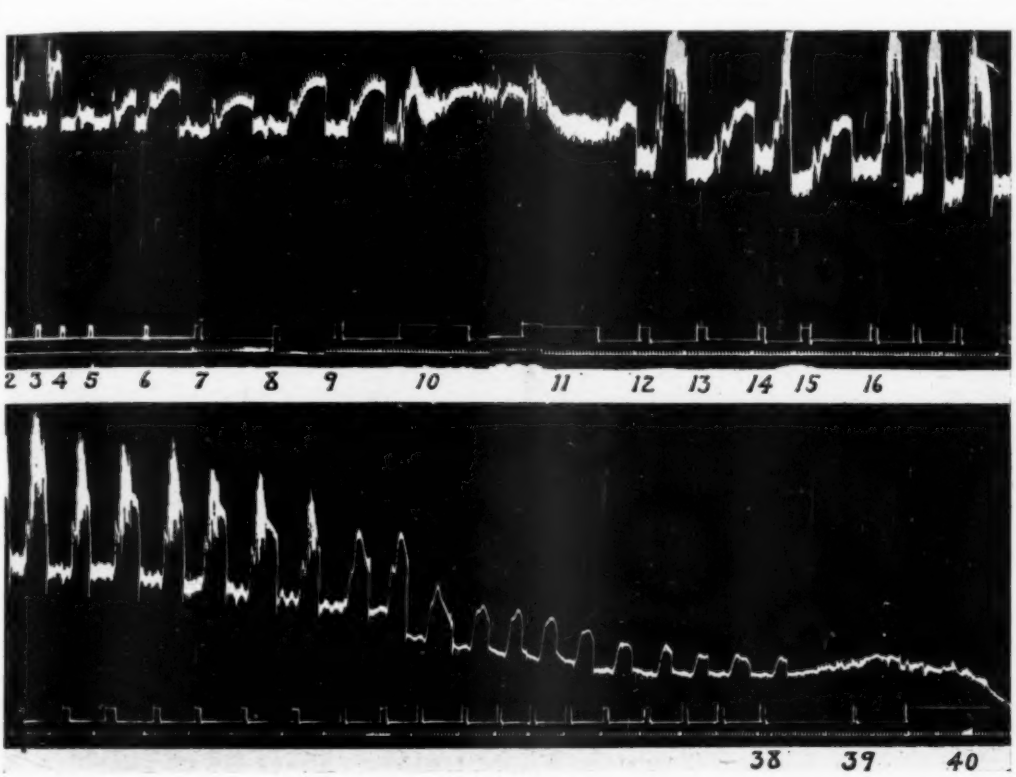


Fig. 13.—The effect of scalding on the vascular response of a dog to adrenalin and Tyramine. *2-3*, Adrenalin, 0.3 c.c. 1:10,000; *4*, Tyramine 1.0 mg.; *5-9*, Tyramine 2.0 mg.; *10-11*, scalded; *12*, adrenalin; *13*, Tyramine; *14*, adrenalin; *15*, Tyramine; *16-38*, adrenalin; *39*, Tyramine; *40*, plasma infusion. (From Page, I. H.: Am. J. Physiol. **142**:366, 1944.[14])

(Fig. 14). Thus if our experiments have sampled fairly, the entire musculature of the vascular system appears to participate in this gradual loss of responsiveness as shock develops.

Probably less significant is the observation that administration of either the antihistaminic, Benadryl, or the metal-containing enzyme depressant, BAL, in sufficient doses, reduces or altogether blocks the action of a variety of stimulating drugs. The arterial pressure often may be maintained at normal levels in such animals for thirty minutes or more (Fig. 15), but sudden and fatal fall in blood pressure may occur at any time without warning. Much the same phenomenon has been observed in shocked animals.

Thus, while it appears that blood vessels and heart, able to respond actively to chemical stimulation, aid in the fight for survival against shock, maintained responsiveness is only one of many factors.

Just what significance to attribute to the work initiated by Chambers and Zweifach,[47] and carried on by Shorr and Zweifach, concerning the appearance in the blood of vasoexcitor and depressor materials, it is, in my opinion, pre-

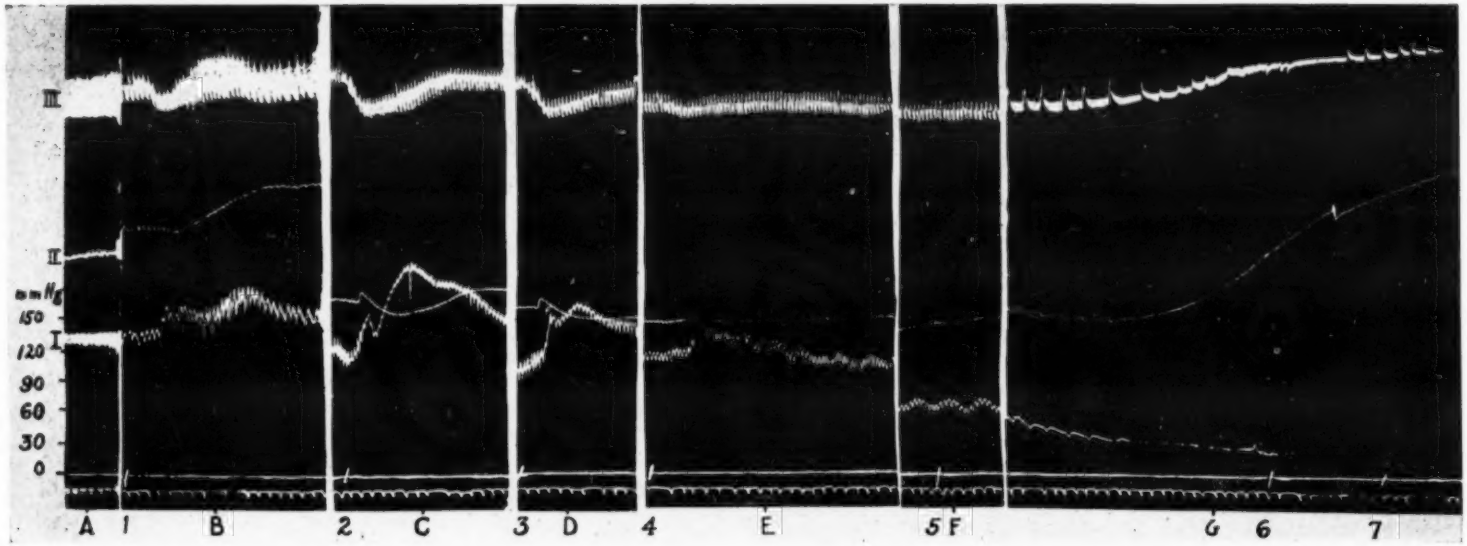


Fig. 14.—*I*, Arterial pressure measured in carotid artery by a mercury manometer. *II*, Intrathoracic venous pressure measured by a water manometer. *III*, Cardiac output measured by cardiometer. Cardiometer used at normal intrathoracic pressure. Lower border of tracing is the systolic volume; upper border is the diastolic volume.

Section *A*: Control period; drum moving slowly. Section *B*: Control period; drum moving fast. *1*, 0.4 c.c. 1:10,000 adrenalin. Section *C*: one hour and ten minutes after abdomen, back, and hind legs were burned. *2*, 0.4 c.c. 1:10,000 adrenalin. Section *D*: Fifty minutes elapsed between *C* and *D*. *3*, 0.4 c.c. 1:10,000 adrenalin. Section *E*: Three hours after *D*. *4*, 0.4 c.c. 1:10,000 adrenalin. Section *F*: Ten minutes after *E*. *5*, 0.5 c.c. 1:10,000 adrenalin. Section *G*: Fifteen minutes after *F*. *6*, 0.4 c.c. 1:10,000 adrenalin. *7*, 0.4 c.c. 1:10,000 adrenalin. (From Page, I. H.: Am. J. Physiol. **142**:366, 1944.[14])

mature to judge. It is an interesting and imaginative investigation, but so far lacks cogent proof of its actual participation in the mechanism of shock.

It has been of some interest to follow the change in vascular capacity for fluid, such as saline or blood, during changes in vascular responsiveness. The pressure in the reservoir is set at 100 to 120 mm. Hg, the connection with the femoral artery opened, and the output or intake registered by the movements of the reservoir. Perhaps the most common picture after scalding is a rapid uptake of fluid from the reservoir, followed by slowing and even some output of blood from the animal to the reservoir. As vascular reactivity fails, the uptake increases rapidly, until during the last thirty minutes of life, the uptake is great. A small dog may take up 2.0 liters or more in this short span. The changing balance of fluid in the reservoir and in the vascular system proved quite a reliable guide to prognosis in these experiments.

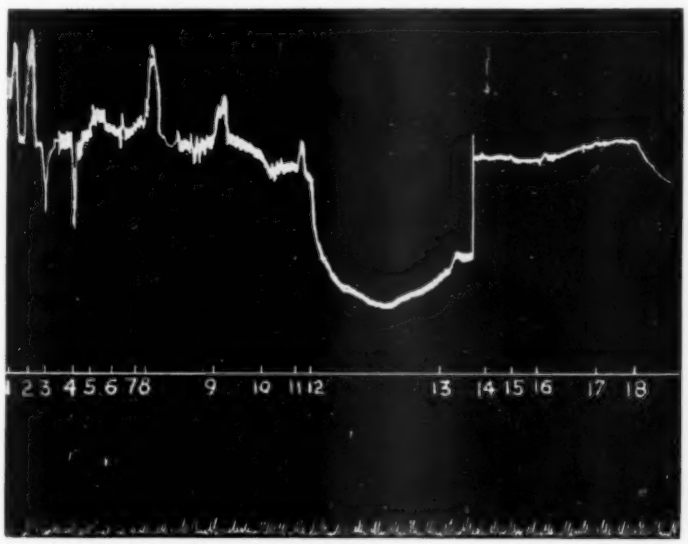


Fig. 15.—Refractoriness produced by large doses of BAL. *1-2*, Adrenalin; *3-4*, histamine; *5*, barium chloride; *6-7*, emulsion of BAL intraperitoneally; *8*, adrenalin; *9*, pure BAL, 1 c.c. intraperitoneally; *10*, adrenalin; *11*, 0.5 c.c. BAL; *12-13*, adrenalin; *14*, histamine; *15-17*, adrenalin; *18*, barium chloride.

The response of supposedly normal dogs to equilibration of their circulation with a pressure reservoir is interesting and often unexpected. The usual animal may take up from 500 to 1,000 c.c. in thirty minutes, or none at all, from the reservoir if the pressure is set about 20 mm. Hg above its own average. Then uptake slows, and for a period from two to twelve hours either some blood may be forced into the reservoir or the uptake amount to some 200 c.c. per hour. On the other hand, some animals immediately take up a liter or more, and the adrenalin response and blood pressure falls as soon as the connection with the reservoir is closed. The uptake of fluid then increases rapidly, reaching 500 c.c. or more in ten minutes. Circulation fails quickly.

The reason for the differences among these "normal" dogs is not known to us, striking as the differences be (Fig. 16).

Certainly vascular responsiveness is not the only, if, indeed, the most important factor in the changed relationship between intake and output of fluid. When adequate fluid is given by this method, responsiveness is maintained in these animals long after it is lost in animals receiving no fluids. But maintenance of some degree of responsiveness does not insure survival of the animals. It only weighs in its favor, just as lack of rapid uptake of fluid by the animal similarly weighs against survival.

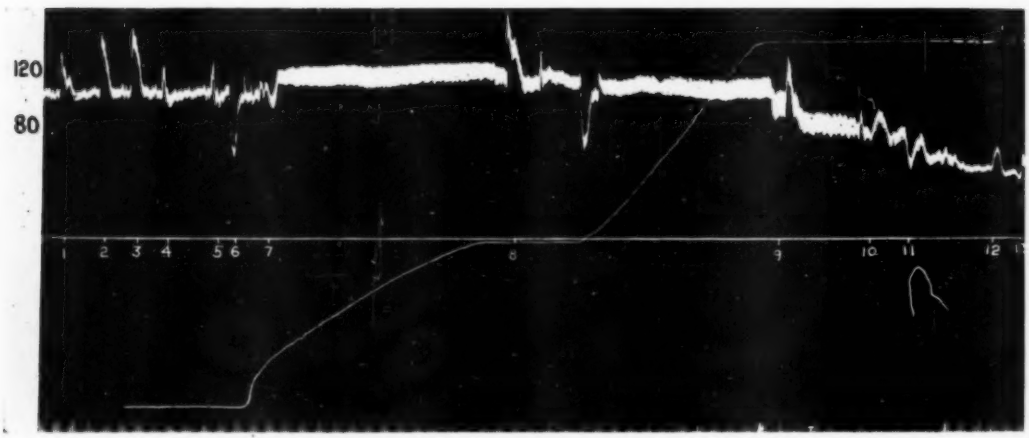


Fig. 16.—Rapid uptake of fluid and early circulatory failure in a supposedly normal dog. *1-3*, Adrenalin; *4-5*, nicotine; *6*, histamine; *7*, reservoir opened at 120 mm. Hg; *8*, adrenalin; *9*, nicotine; *10*, histamine; *11*, adrenalin; *12*, nicotine; *13*, adrenalin; 400 c.c. in first ten minutes and 600 c.c. in next ten minutes.

INTRA-ARTERIAL TRANSFUSION

There is one factor in the treatment of shock on which all will agree: blood volume must be restored to normal in as short a time as possible. In the terminal phase, every minute counts. Since blood has become easily available, the remaining problem is how to give it most effectively.

The principle of giving blood by artery extends well back into the annals of physiology, and was used in a few patients by Halstead and George Crile. But the technical difficulties were not solved, nor were the reasons for its use in this fashion understood, and so the method was discarded. Early in the war, Colonel Sam Seeley, U. S. A., suggested to us that the problem be investigated, and thus began our work on the subject in 1941, first with Dr. K. G. Kohlstaedt[13,46] and later with Dr. Otto Glasser.[48]

Among the reasons for giving blood by artery instead of by vein are the following:

1. Blood pressure is restored to normal levels within a few minutes, and the pressure is controllable.

2. Blood volume deficits are automatically corrected. That amount of blood will be taken into the circulation which is required to fill it at a given arterial pressure.

3. When the heart and respiration have failed, blood given into an artery often brings about resuscitation.

Other reasons will be discussed later. The important thing to remember is that a secondary heart provides pressure to fill the vascular tree and maintain pressure in it.

The apparatus required is simple. For animals, Fig. 2 gives an idea of how it is set up. For human beings, it is much simpler, consisting merely of a pressure reservoir with a manometer connected to the femoral or radial artery (Fig. 17). If the need is urgent, an 18 gauge needle may be inserted, point-

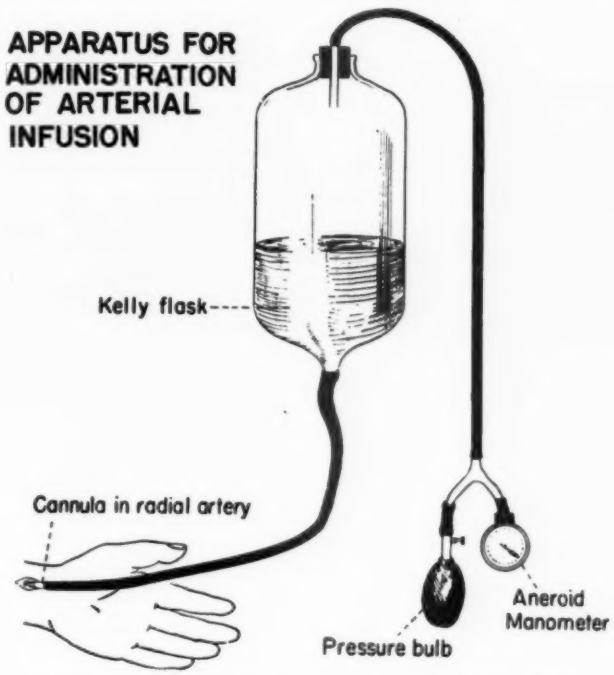


Fig. 17.—Simple apparatus for emergency arterial transfusion.

ing toward the heart, or a glass cannula may be tied in if time permits. Heparin solution is used to prevent coagulation in the cannula and tubing, but the blood itself in the reservoir may be citrated unless very large amounts are to be given, when the use of heparin becomes more desirable. Murphy drips, or any sort of contrivance which might trap air, are carefully to be avoided as there is always danger of air embolism when blood enters the arterial circulation at a fast rate. I need not trouble you with the details of the procedure which I have described elsewhere.[59] Dr. Donald Hale of the Department of Anesthesiology of the Cleveland Clinic has now had a wide experience in the use

of this method on patients. Suffice it to say that the procedure is extremely simple, the apparatus is mobile, and nothing that is not ordinary hospital equipment need be used. But if the method is to be used, assemblies of the apparatus must be ready on every floor of a hospital for emergencies such as exsanguination and resuscitation.

In practice, if the blood pressure is 30 mm. Hg or less, the pressure in the reservoir should be set 20 mm. higher, and blood allowed to flow in. The pressure is then raised in increments of 20 mm. until the systemic pressure is 100 mm. of mercury. It is seldom advisable to raise the pressure higher, as irregularities of the heartbeat and signs of embarrassment of the circulation often develop at higher pressures. It may be desirable to leave the patient's artery open to the reservoir at this pressure for a time, until it is reasonably sure that the pressure will hold.

A fact of interest that we observed some time ago[13] was that given by artery, little more than half the amount of blood was required to restore arterial pressure than when blood was given by vein. Perhaps the important

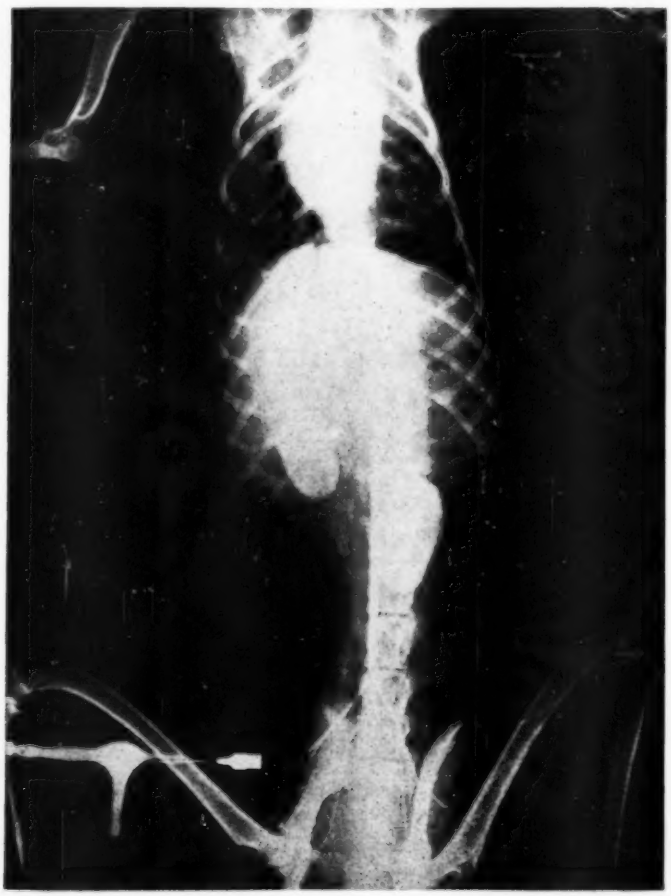


Fig. 18.—Intra-arterial infusion of Skiodan into the femoral artery of a dog deeply in shock, with extreme hypotension. Note that the kidneys fill first.

thing to remember is that in case of emergency it makes little difference what fluid is administered to keep the circulation going until the more suitable blood is available. To wait for blood to be brought from the blood bank and warmed to body temperature is to lose a life.

There are a number of interesting observations that have been made during the course of this work. The one that interested me most was that at low systemic pressures blood flows retrograde up the aorta and perfuses the coronary and medullary vessels. We had noticed on several occasions that, very shortly after the infusion was started in patients who had ceased breathing, a deep breath was taken. With the help of Dr. Robert Hughes of the Cleveland Clinic, we took serial x-ray photographs of a dog deeply in shock while it was receiving an arterial transfusion of radiopaque material. They showed that the kidneys filled first, and immediately thereafter the coronary and the medullary circulations (Figs. 18 and 19). One could hardly wish for finer photographs of the coronary vessels!

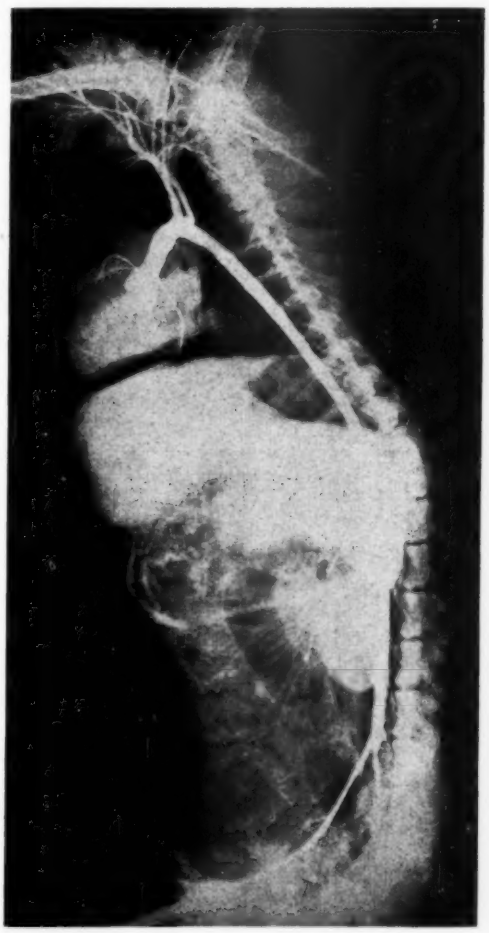


Fig. 19.—Same animal as in Fig. 18 a few seconds later. The coronary and medullary vessels have now filled.

This seems to explain why we were able to resuscitate, with a combination of intra-arterial infusion of blood and adrenalin and artificial respiration, animals in which circulation and respiration had ceased.

Thirty-nine experiments on dogs were performed by Glasser in which, after the usual hemorrhagic shock procedure, more blood was withdrawn until the respiration and heart stopped, as indicated by electrocardiographic and pneumographic records.

Respiration stopped first, and was started artificially in from two to eight minutes. When the heart had stopped for about two minutes, treatment by rapid intra-arterial transfusion, along with adrenalin and ouabain, was begun. Enough heparin had entered the animal's circulation to reduce the possibility of coagulation of the blood.

Eighty-four per cent of the animals could be resuscitated; 51 per cent lived for an average of ten hours, and 33 per cent survived, apparently unharmed, indefinitely. An example of one of these experiments is given in Fig. 20. Obviously, an intravenous transfusion would not have been useful.

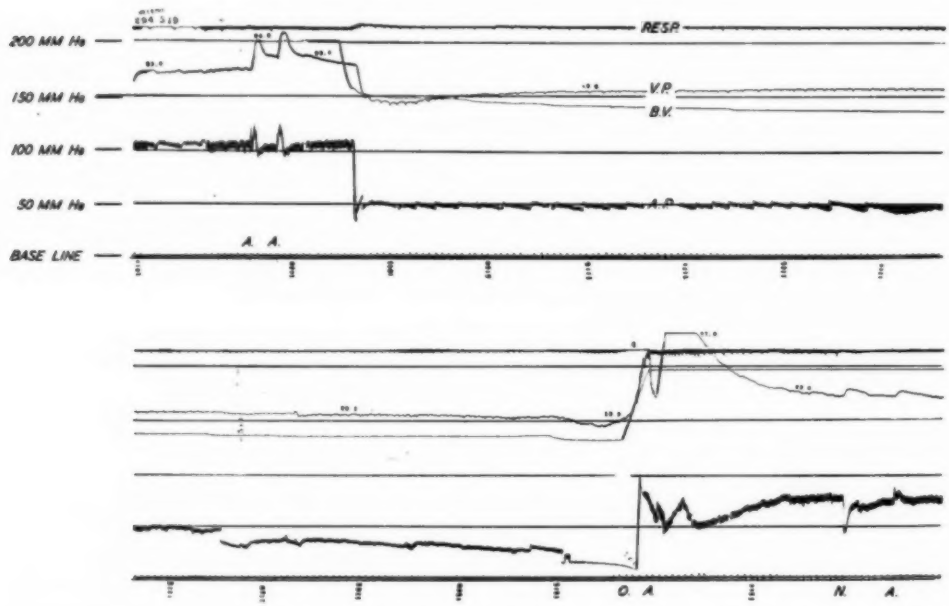


Fig. 20.—Resuscitation of a dog which had been subjected to the shock procedure, and then bled until heart (two and one-half minutes) and respiration (four minutes) stopped. Arterial transfusion plus ouabain and adrenalin given at *O.A.* The animal survived.

Also of interest is the fact that it was possible, in patients, to locate bleeding vessels in the abdomen which no longer bled and hence were lost to sight when the pressure had fallen to a very low level. When the pressure was raised for a minute or so, blood spurted from the broken vessel, allowing its ligation.[49] On a number of occasions, this maneuver has proved itself useful (Fig. 21).

Dr. James Gardner[50] has used the procedure in some fifty patients to reduce the risk of severe blood loss during cranial operations. With Dr. Donald Hale he has transferred about 2.0 liters of blood to reservoir bottles and re-

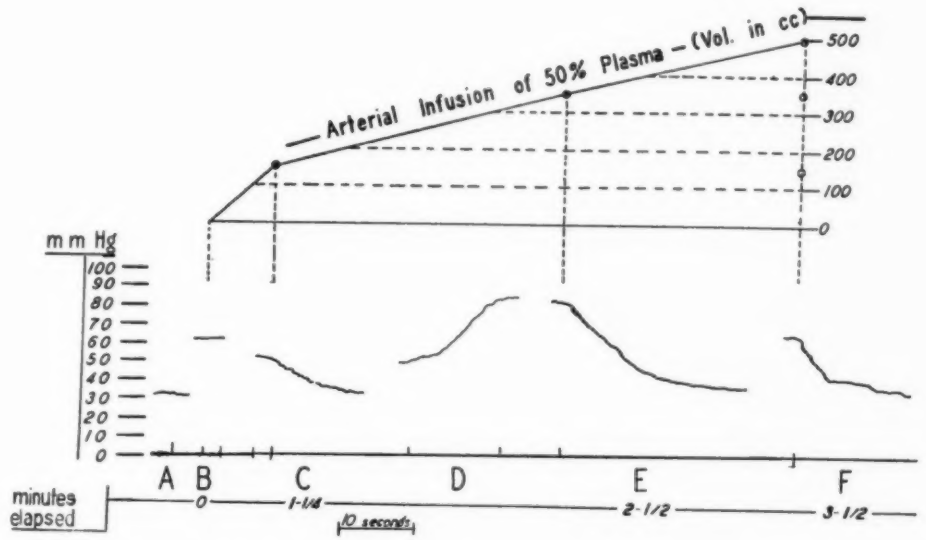


Fig. 21.—Example of the effect of intra-arterial infusion in a patient in deep shock with undiagnosed abdominal bleeding. Arterial pressures are recorded on a kymograph. *A*, Initial pressure; *B*, pressure during intra-arterial infusion; *C*, infusion was discontinued and pressure fell off rapidly; *D*, reinstituted; *E*, infusion stopped; *F*, same sequence repeated. Clearly blood was leaking rapidly from the vascular tree. (Kohlstaedt and Page.)

duced the blood pressure to 80 or 90 (Fig. 22). Their experience shows that, at this level, bleeding in the brain is greatly reduced and operation materially facilitated. This is especially true with such tumors as olfactory groove meningiomas, where the pedicle is not reached until the bulk of the tumor is already cut away. Bleeding may be severe and dangerous. The operating time may be reduced to less than half and blood loss to insignificance. Before the cavity is closed, the patient again receives all but 500 c.c. of his blood; this may be given later, intravenously, if needed.

Dr. Harold Harris[51] has also used the procedure for induced hypotension in some fifty cases to lessen hemorrhage during a critical stage in the fenestration operation. He believes his results more secure when at one point in the operation blood is removed and replaced as soon as the dangers of hemorrhage are past.

In dogs, we have avoided many of the great and sometimes disastrous falls in blood pressure when operations are being performed on the aorta. By judicious removal of blood when the aorta is being closed, and its rapid readmission when the aorta is being opened, significant changes in arterial pressure may be almost wholly avoided. Kay[52] has described the use of this procedure to maintain life while suturing stab wounds in the heart.

It must be evident to any thoughtful person that arterial transfusion has specific and limited application. It obviously does not replace intravenous transfusion except under special conditions. Nor can its use for induced hypotension in surgery be profitable except where there is definite indication for the procedure, and where the anesthetist has had experience in its use. On the

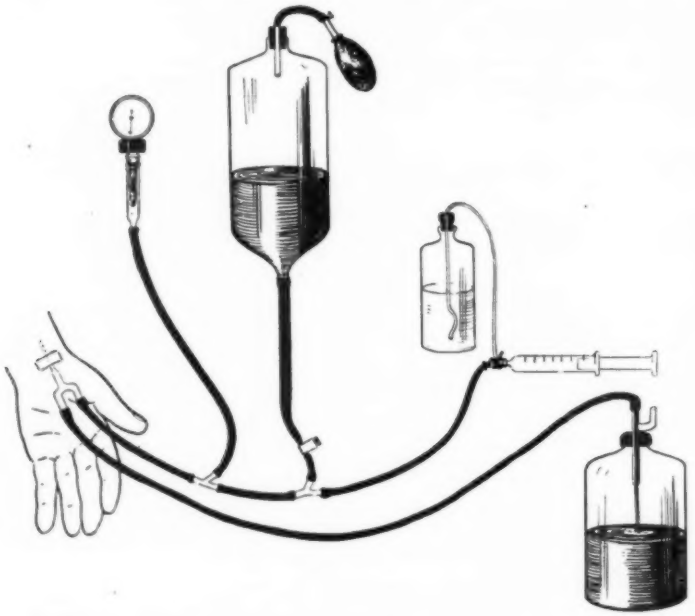


Fig. 22.—Apparatus used for induced hypotension in patients. The syringe and small bottle contain heparin solution to prevent coagulation in the tubing.

other hand, in certain circumstances, such as deep shock, resuscitation, exsanguination, location of bleeding vessels, and operations in which blood loss may be serious, it may prove invaluable. If it does nothing else but call the attention of the physician to the necessity of speed in the treatment of shock, it will have served a real purpose.

REFERENCES

1. Gesell, R.: Studies on the Submaxillary Gland. III. Some Factors Controlling the Volume-Flow of Blood, Am. J. Physiol. **47**:438, 1918.
2. Page, I. H., Taylor, R. D., and Kohlstaedt, K. G.: A Case of Extreme Hypotension Following Acute Arsenic Poisoning With Adequate Blood Supply to the Tissues, Am. J. Med. **205**:730, 1943.
3. Blalock, A.: Principles of Surgical Care, Shock and Other Problems, St. Louis, 1940, The C. V. Mosby Company.
4. Parsons, E., and Phemister, D. B.: Hemorrhage and "Shock" in Traumatized Limbs, an Experimental Study, Surg., Gynec. & Obst. **51**:196, 1930.
5. Gregersen, M. I.: Symposium on Physiological Contributions to War Problems; Physiological Contributions to Problem of Shock, Federation Proc. **5**:354, 1946.
6. Gibson, J. G., Seligman, A. M., Peacock, W. C., Aub, J. C., Fine, J., and Evans, R. D.: Distribution of Red Cells and Plasma in Large and Minute Vessels of Normal Dogs Determined by Radioactive Isotopes of Iron and Iodine, J. Clin. Investigation, **25**:848, 1946.

7. Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersen, M. I., and Richards, D. W., Jr.: Studies of Circulation in Clinical Shock, Surgery **13**:964, 1943.
8. Wilhelmi, A. E.: Metabolic Aspects of Shock, Ann. Rev. Physiol. **10**:259, 1948.
9. McMichael, J.: Clinical Aspects of Shock, J. A. M. A. **124**:274, 1944.
10. Howarth, S., and Sharpey-Schafer, E. P.: Low Blood Pressure Phases Following Haemorrhage, Lancet **1**:18, 1947.
11. Glasser, O., and Page, I. H.: Experimental Hemorrhagic Shock; A Study of Its Production and Treatment, Am. J. Physiol. **154**:297, 1948.
12. Wiggers, C. J., and Werle, J. M.: Explanation of Method for Standardizing Hemorrhagic Shock, Proc. Soc. Exper. Biol. & Med. **49**:604, 1942.
13. Kohlstaedt, K. G., and Page, I. H.: Hemorrhagic Hypotension and Its Treatment of Intra-arterial and Intravenous Infusion of Blood, Arch. Surg. **47**:178, 1943.
14. Page, I. H.: Cardiovascular Changes Resulting From Severe Scalds, Am. J. Physiol. **142**:366, 1944.
15. Page, I. H., and Abell, R. G.: The State of the Vessels of the Mesentery in Shock Produced by Constricting the Limbs and the Behavior of the Vessels Following Hemorrhage, J. Exper. Med. **77**:215, 1943.
16. Page, I. H., and Abell, R. G.: Effects of Acute Hemorrhage and of Subsequent Infusion Upon the Blood Vessels and Blood Flow as Seen in the Mesenteries of Anesthetized Dogs, Am. J. Physiol. **143**:182, 1945.
17. Abell, R. G., and Page, I. H.: A Study of the Smaller Blood Vessels in Burned Dogs and Cats, Surg., Gynec. & Obst. **77**:348, 1943.
18. Wiggers, C. J., Opdyke, D. F., and Johnson, J. R.: Portal Pressure Gradients Under Experimental Conditions, Including Hemorrhagic Shock, Am. J. Physiol. **146**:192, 1946.
19. Selkurt, E. E., Alexander, R. S., and Patterson, M. B.: Role of Mesenteric Circulation in Irreversibility of Hemorrhagic Shock, Am. J. Physiol. **149**:732, 1947.
20. Opdyke, D. F., and Foreman, R. C.: A Study of Coronary Flow Under Conditions of Hemorrhagic Hypotension and Shock, Am. J. Physiol. **148**:726, 1947.
21. Corcoran, A. C., and Page, I. H.: Effects of Hypotension Due to Hemorrhage and of Blood Transfusion on Renal Function in Dogs, J. Exper. Med. **78**:205, 1943.
22. Phillips, R. A., Dole, V. P., Hamilton, P. B., Emerson, K., Jr., Archibald, R. M., and Van Slyke, D. D.: Effect of Acute Hemorrhage and Traumatic Shock on Renal Function of Dogs, Am. J. Physiol. **145**:314, 1946.
23. Selkurt, E. E.: Renal Blood Flow and Renal Clearance During Hemorrhagic Shock, Am. J. Physiol. **145**:699, 1946.
24. Lauson, H. D., Bradley, S. E., and Cournand, A.: The Renal Circulation in Shock, J. Clin. Investigation **23**:381, 1944.
25. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Immediate Effects on Renal Function of the Onset of Shock Due to Partially Occluding Limb Tourniquets, Ann. Surg. **118**:871, 1943.
26. Bywaters, E. G. L., and Beall, D.: Crush Injuries With Impairment of Renal Function, Brit. M. J. **1**:427, 1941.
27. Corcoran, A. C., and Page, I. H.: Post-traumatic Renal Injury—Summary of Experimental Observations, Arch. Surg. **51**:93, 1945.
28. Corcoran, A. C., and Page, I. H.: Crush Syndrome, Post-traumatic Anuria—Observations on Genesis and Treatment, J. A. M. A. **134**:436, 1947.
29. Maegraith, B. G., Havard, R. E., and Parsons, D. S.: Renal Syndrome of Wide Distribution Induced Possibly by Renal Anoxia, Lancet **2**:293, 1945.
30. Lucké, B.: Lower Nephron Nephrosis: The Renal Lesions of the Crush Syndrome, of Burns, Transfusions and Other Conditions Affecting the Lower Segment of the Nephron, The Military Surgeon **99**:371, 1946.
31. Mallory, T. B.: Hemoglobinuric Nephrosis in Traumatic Shock, Am. J. Clin. Path. **17**:427, 1947.
32. Little, J. M., Green, H. D., and Hawkins, J. E., Jr.: Evidence From Crosstransfusion Experiments That Diminished Urine Flow Accompanying Ischemic Compression Shock Is not Due to Humoral Factors, Am. J. Physiol. **151**:554, 1947.
33. (a) Page, I. H.: The Occurrence of a Vasoconstrictor Substance in Blood During Shock Induced by Trauma, Hemorrhage and Burns, Am. J. Physiol. **139**:386, 1943.
    (b) Seelig, M. G., and Joseph, D. R.: On the Condition of the Vaso-Constrictor Center During the Development of Shock, J. Lab. & Clin. Med. **1**:283, 1915.

34. Alrich, E. M.: Studies on Burns. II. Observations on a Vasoconstrictor Substance in Lymph From a Burned Area, Surgery **15**:908, 1944.

35. Sapirstein, L. A., Ogden, E., and Southard, F. D., Jr.: Renin-like Substance in Blood After Hemorrhage, Proc. Soc. Exper. Biol. & Med. **48**:505, 1941.

36. Collins, D. A., and Hamilton, A. S.: Changes in the Renin-Angiotonin System in Hemorrhagic Shock, Am. J. Physiol. **140**:499, 1943.

37. Huidobro, F., and Braun-Menendez, E.: Secretion of Renin by Intact Kidney, Am. J. Physiol. **137**:47, 1942.

38. Rapport, M., Green, A. A., and Page, I. H.: Serum Vasoconstrictor. IV. Isolation and Characterization, J. Biol. Chem. **176**:1243, 1948.

39. Rapport, M., Green, A. A., and Page, I. H.: Crystalline Serotonin, Science **108**:329, 1948.

40. Rapport, M., Green, A. A., and Page I. H.: Partial Purification of the Vasoconstrictor in Beef Serum, J. Biol. Chem. **174**:735, 1948.

41. Wiggers, C. J.: Myocardial Depression in Shock; Survey of Cardiodynamic Studies, Am. Heart J. **33**:633, 1947.

42. Page, I. H.: Participation of the Heart in Shock, Mod. Concepts Cardiovas. Dis. **16**:1 Am. Heart Assoc., New York, 1947.

43. Wiggers, H. C., Ingraham, R. C., Roemhild, F., and Goldberg, H.: Vasoconstriction and the Development of Irreversible Hemorrhagic Shock, Am. J. Physiol. **153**:511, 1948.

44. Page, I. H., and Taylor, R. D.: Mechanism of Renin Tachyphylaxis—Restoration of Responsiveness by Tetraethyl Ammonium Ion, Science **105**:622, 1947.

45. Freeman, N. E., Shaffer, S. A., Schecter, A. E., and Holling, H. E.: Effect of Total Sympathectomy on Occurrence of Shock From Hemorrhage, J. Clin. Investigation **17**:359, 1938.

46. Kohlstaedt, K. G., and Page, I. H.: Terminal Hemorrhagic Shock; Circulatory Dynamics, Recognition and Treatment, Surgery **16**:430, 1944.

47. Chambers, R., and Zweifach, B. W.: Blood-borne Vasotropic Substances in Experimental Shock, Am. J. Physiol. **150**:239, 1947.

48. Glasser, O., and Page, I. H.: Experimental Hemorrhagic Shock; A Study of Its Production and Treatment, Am. J. Physiol. **154**:297, 1948.

49. Page, I. H.: Treatment of Shock by Intra-arterial Infusion, Bull. U. S. Army M. Dept. **7**:366, 1947.

50. Gardner, W. J.: The Control of Bleeding During Operation of Induced Hypotension, J. A. M. A. **132**:572, 1946.

51. Harris, H. E., and Hale, D. E.: Induced Hypotension in the Control of Bleeding During the Fenestration Operation, Tr. Am. Acad. Ophth. 90, 1947.

52. Kay, E. B., and Hacker, V. D.: The Treatment of Shock by Aortic Transfusion During Thoracic Operations, J. A. M. A. **134**:604, 1947.

53. Robertson, O. A., and Bock, A. V.: Memorandum on Blood Volume After Haemorrhage, Med. Res. Comm. Special Report, Series No. 25, London, 1919, His Majesty's Stationery Office.

54. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Haemorrhage, Med. Res. Comm. Special Report, Series No. 27, London, 1919, His Majesty's Stationery Office.

55. Bobb, J. R. R.: Role of Kidney in Resistance to Ischemic Compression Shock, Federation Proc. **6**:78, 1947.

56. Hechter, O., Bergman, H. C., and Prinzmetal, M.: Role of Renal Pressor System in Burn Shock, Am. Heart J. **29**:493, 1945.

57. Moon, V. H.: Renal Deficiency Associated With Shock, J. A. M. A. **134**:425, 1947.

58. Green, H. D., Lewis, R. N., Nickerson, N. D., and Heller, A. L.: Blood Flow, Peripheral Resistance and Vascular Tonus, With Observations on Relationship Between Blood flow and Cutaneous Temperature, Am. J. Physiol. **141**:518, 1944.

59. Page, I. H.: Arterial Transfusion, Practitioner **161**:479, 1948.

60. Phemister, D. B., Eichelberger, L., and Lacstar, C. H.: Early Effects on Dogs of Section of the Eighth Cervical Segment of the Spinal Cord and Their Bearing on Shock, Arch. Surg. **51**:32, 1945.

61. Reinhard, J. J., Glasser, O., and Page, I. H.: Hemorrhagic Hypotension in Hepatectomized and Bilaterally Nephrectomized Dogs, Am. J. Physiol. **155**:106, 1948.

VENTRICULAR FIBRILLATION INDUCED BY COLD

H. E. Hoff, M.D., and H. Stansfield, M.D.
Houston, Texas

A BRIEF direct-current pulse of suprathreshold strength applied to the ventricle late in systole or early in diastole (the "vulnerable period") may often initiate ventricular fibrillation. Fibrillation does not, however, begin immediately, but follows a brief tachysystolic episode during which the stimulated region, acting as a pacemaker, sends out impulses at an accelerating tempo. Fibrillation is a consequence of this tachycardia, and follows any similar tachycardia however generated, whether by low-voltage alternating current stimulation, by rapid induction-shock stimulation, or from discharge of an ectopic focus after occlusion of a coronary artery or drug administration.[1,2,3] The problem of the "vulnerable period" is thus resolved, not into a question of genesis of fibrillation, but into one of the origin of continuing pacemaker activity at the stimulated region. Thus far, however, no reasons have been advanced why stimulation during the "vulnerable period," and only during this period, should induce pacemaker activity.

When the whole body of the dog or cat is cooled, the heart appears to be more than normally susceptible to the development of ventricular fibrillation. When, instead of the whole heart, a portion only is cooled, by means of a thermode applied to it in situ, the ventricles are rendered even more highly sensitive to fibrillation, which can then almost invariably be produced by mechanical or electrical stimulation which normally would have no effect beyond eliciting ventricular extrasystoles.

The experiments reported here, designed to elucidate the mechanism of ventricular fibillation as elicited in hearts locally cooled, appear to afford a new approach to the nature of the "vulnerable period."

METHOD

The basic techniques employed in these experiments were as follows: (a) A small (1.0 cm. in diameter) area of the heart was cooled locally by inserting between the heart and pericardium a small, flat thermode through which water at an appropriate temperature could be circulated. Although fibrillation could be evoked by cooling any part of the ventricles, in all of the experiments reported here the cooling was restricted to the lateral wall of the left ventricle,

From the Department of Physiology, Baylor University College of Medicine, Houston, Texas, and the Department of Physiology, McGill University, Montreal, Canada.
These studies were supported by a grant from the Life Insurance Medical Research Fund.

near the apex. (b) The stimuli employed were in all cases slightly supraliminal induction shocks, applied to the ventricle as far as possible away from the cooled region, usually, therefore, at the right lateral base. Because of the distance of the cooled region from the region stimulated, and the strength of the shocks, it can safely be assumed that the shocks were without direct electrical influence upon the cooled area. Moreover, similar results could be obtained by mechanical stimulation of the right ventricle. It is therefore likely that the sole influence of the stimulation on the cooled area was exerted by means of impulses propagated thereto through the ventricular myocardium or other conductive tissue. (c) Electrocardiograms were taken with CV leads, with the chest electrode directly external to the thermode placed at the left apex. The use of this lead makes it possible to locate with some accuracy the point of origin of ectopic ventricular beats, particularly those arising directly beneath the exploring chest electrode, which show exclusively a QS wave as the initial complex. Extrasystoles originating in distant areas exhibit a simple R configuration (Fig. 1), while those from intermediate areas possess Q, R, and S waves of varying amplitudes, Q and S being larger, and R smaller in proportion as the point of origin nears the chest electrode. Other chest leads are equally useful for this purpose, but the standard limb leads permit localization only if Leads I and III are recorded simultaneously.

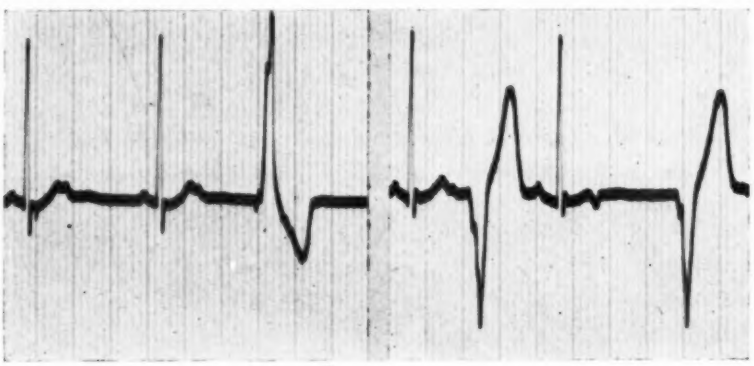


Fig. 1.—C V lead with the chest electrode on the left chest immediately over the left apex. On the left is a single ventricular extrasystole evoked by stimulation at the lateral margin of the right base, showing a simple R as its initial complex. On the right are two responses to stimulation at the left apex, showing the QS configuration characteristic of extrasystoles arising directly beneath the chest electrode.

Employing the above techniques of cooling, stimulating, and recording, two series of experiments were carried out in fifteen dogs anesthetized with Nembutal, curarized, and ventilated by intratracheal oxygen under slight positive pressure. In the first series, a rhythmic series of single induction shocks was applied to the normally beating and uncooled heart at intervals of one to two seconds. Out of phase with the beat of the heart, they fell at random throughout the cardiac cycle, evoking ventricular extrasystoles whenever they coincided with an excitable part of the cycle. When the whole of a normal

cardiac cycle had been thoroughly explored, stimulation was stopped and cooling started. The electrocardiograph was then started and stimulation reinstituted.

To avoid the interference of supraventricular and ectopic beats (see Fig. 6) and thus simplify analysis, a second series of experiments was devised in which all supraventricular beats were inhibited by stimulation of the vagus, potentiated by physostigmine, to permit maximal reduction of stimulus intensity and thus prevent obscuring the record by artifacts. Against a background of cardiac arrest, paired induction shocks were delivered to the right ventricle by a Lucas pendulum.

RESULTS

Single Impulses in the Normal Cycle.—In no case did ventricular fibrillation follow a single induction shock in uncooled hearts, regardless of the phase of the cardiac cycle in which it was delivered, and whether or not it evoked a response. When responses to stimulation did occur they were characterized electrocardiographically by simple upright initial complexes or R waves interrupting the normal rhythm and followed usually by compensatory pauses. In rare instances they were followed by a single additional ectopic beat of identical configuration, representing, therefore, a spontaneous beat arising from the area of stimulation. (Even induction shocks, if excessively strong, can induce ventricular fibrillation following repetitive responses of the stimulated region, but direct current pulses of somewhat longer duration than induction shocks are far more suitable for its production.)

Single responses to stimulation when the heart was cooled also indicated their distant origin by their simple R configuration. When late in the cycle, or when the cooling was insufficient (above 10° C. in the reservoir of cooling fluid), they were the sole ectopic manifestations, and the results were no different from those in controls with the heart at normal temperature. When, however, the temperature of the cooling fluid was below 10° C., and the extrasystole was evoked early in the recovery cycle, the induced extrasystole was followed by one or more spontaneous extrasystoles whose origin from the cooled area was indicated by a simple QS pattern in direct contrast to the R wave of the electrically induced extrasystole (Fig. 2). These spontaneous extrasystoles at times ceased after one or more beats, but in the majority of experiments they terminated after one to six beats in ventricular fibrillation (Figs. 3 and 4). Although the point was not clear because of difficulty in controlling both variables in sufficient experiments, it seemed that the spontaneous beats that failed to eventuate in fibrillation followed stimulation later in the cardiac cycle and at less cold temperatures.

Ventricular fibrillation, after a short run of tachycardia, was produced in the second series of experiments when two paired impulses were sent into the cooled area of a quiescent heart at intervals corresponding to the "vulnerable"

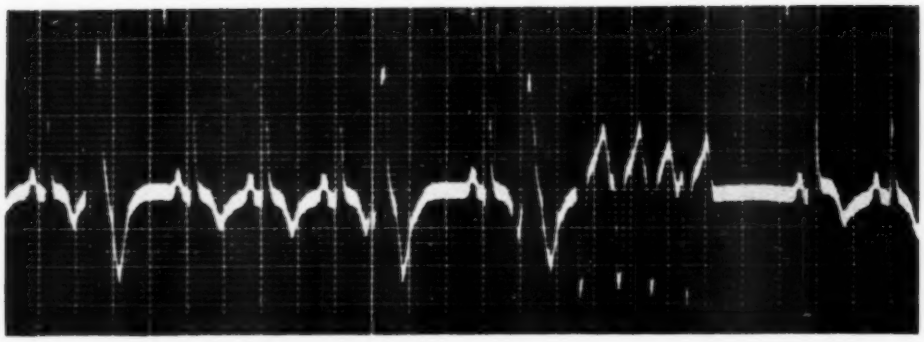


Fig. 2.—C V lead showing a normal cardiac rhythm with a cooled left apex as demonstrated by the inverted T wave. Three ventricular extrasystoles were evoked by stimulation at the right base, and exhibit a characteristic "distal" configuration. The first two are followed only by the expected compensatory pause; the third, which is the earliest of the three in the cycle, is followed by four spontaneous extrasystoles of the very opposite configuration, indicating that they have arisen from the zone of cooling.

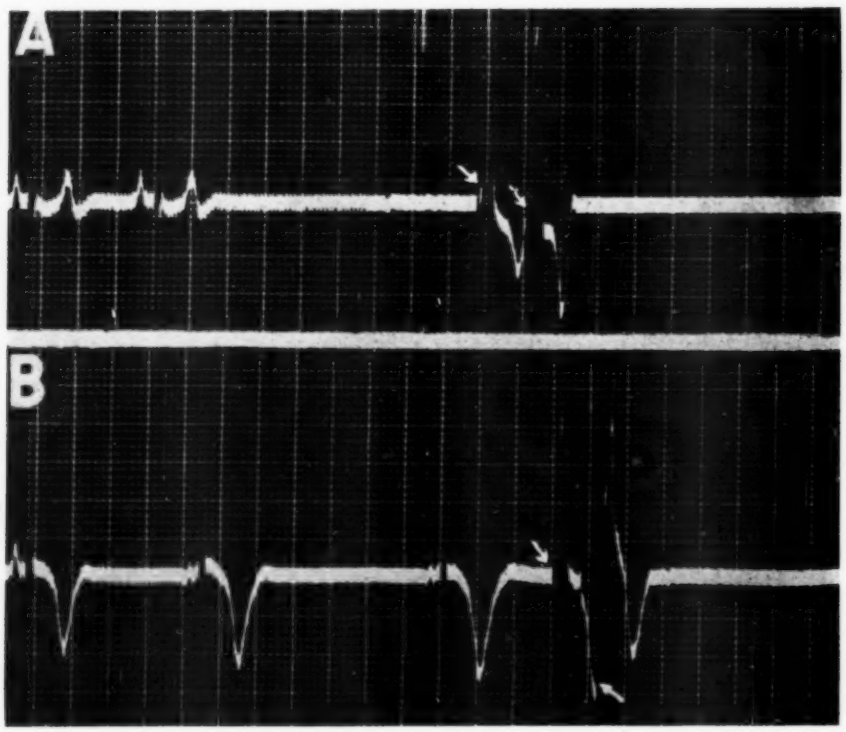


Fig. 3.—*A*. Control, C V lead, normal temperature as shown by upright T waves. Cardiac arrest by vagal stimulation. Two stimuli at an interval of 0.26 second elicit two responses showing the characteristic R wave of a "distal" extrasystole. *B*, Early cooling in same experiment. Cardiac arrest by vagal stimulation. The two stimuli still evoke solely the two direct responses originating at the stimulated area.

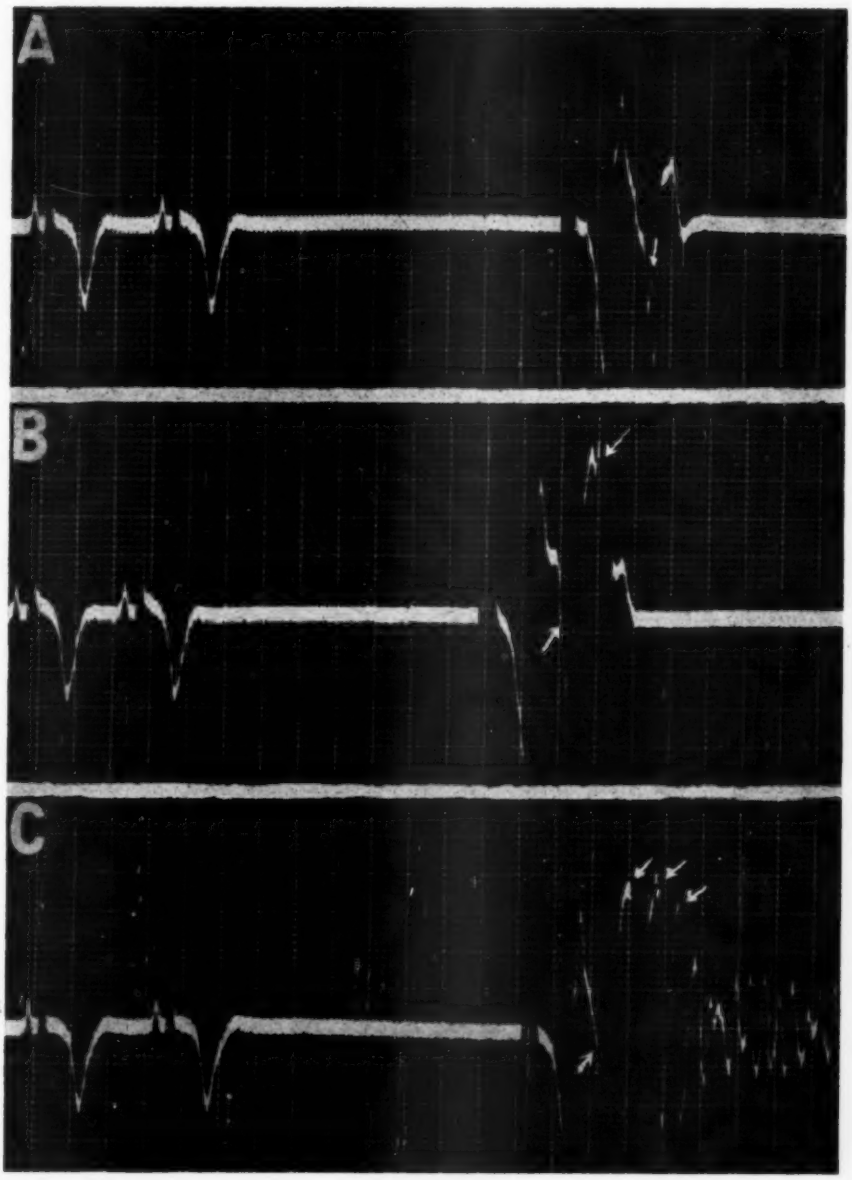


Fig. 4.—Same experiment as shown in Fig. 3., at successively later stages of cooling. *A*, The two "distal" extrasystoles are now followed by a single spontaneous response from the cooled area. It arises (see arrow) on the early rising phase of the second T wave. *B*, Two spontaneous responses marked by arrows follow the two induced responses. *C*, Four spontaneous responses at an accelerating tempo arise in the cooled area and culminate in ventricular fibrillation.

interval between normal and induced beats in the first series. With lesser degrees of cooling, or slightly longer intervals, it was at times possible to produce a single spontaneous beat or a run of tachycardia which did not terminate in fibrillation.

DISCUSSION

These experiments present in a new light, and suggest an explanation for, the phenomenon of the "vulnerable period" of the cardiac cycle, that period of late systole or early diastole during which a supramaximal electrical stimulus may be followed by spontaneous firing from the stimulated region, culminating in ventricular fibrillation. When a brief direct-current pulse is so applied to the heart as to induce pacemaker activity, at least three effects may be produced at the point of stimulation: (a) anodal or cathodal polarization, (b) reduction of accommodation at the anode and increase at the cathode, and (c) a premature response. In fibrillation facilitated by cooling, these factors are separated. The stimulus to the cooled area is in this case only the normal stimulus of a conducted impulse, and while, from the nature of the cardiac monophasic action potential, the advancing impulse might be considered to act toward the cooled area as a brief direct-current pulse of low voltage, it is more probable that it is in this case the early response rather than the early stimulus that conditions the subsequent repetitive firing from the cooled focus. Expressed in another way, following the sense of the second series of experiments, it can be stated that the reason the stimulation in the vulnerable part of the cycle evokes repetitive firing is that it produces paired responses from an irritable focus at a sufficiently short, and probably critical, interval.

The response to this paired discharge of the cooled area is the development there of a new pacemaker, generating a series of beats which, depending on conditions, either stops or leads to fibrillation. Harris and Rojas[3] have stated the reasons for considering that the first few of these beats are in fact separate beats and not already re-entrant beats. To their arguments can be added another, observed in these experiments, namely, that the series may stop after one or more beats without culminating in fibrillation, as De Boer[4,5] has shown in the frog, and as Harris, Moe, and Wiggers[1,2] have demonstrated in the mammal. Because of the extreme infrequency of spontaneous arrest in the fibrillating ventricle of the dog, it is unlikely that the early discharges represent re-entrant beats from a circus motion. This confirms the view that the "vulnerable period" concerns pacemaking behavior primarily, and that the fibrillation that supervenes is a response to the accelerating tachycardia.

Other more indirect evidence is afforded by the almost exact reproduction in these experiments, especially in the second series, of observations of Granit and Skoglund[6] on the effect of cooling the artificial synapse or ephapse. They found that if the sciatic nerve be cut, impulses sent down motor fibers by stimulation of the ventral roots set up "reflected" impulses in the dorsal root fibers by a type of "synaptic" transmission at the cut surface. When this region was cooled, closely paired impulses entering the ephapse evoked not only the

two responses to the "afferent" impulses, but also a spontaneous discharge along the "efferent" fibers arising presumably at the ephapse. In such a preparation there can be no question of circus motion, and the spontaneous discharge can have arisen only from "pacemaker" activity at the ephapse, induced by the arrival there of two closely placed impulses and by the paired responses of the "efferent" limb of the ephapse.

A mechanism that appears able to account for this phenomenon is a combination of two factors: (a) the reduction by cooling of the accommodation of the heart to a constant background stimulus, and (b) the supernormality associated with the negative after-potential. Wedensky first observed the prototype of the latter part of the mechanism in the frog nerve-muscle preparation stimulated subliminally by rapidly repeated shocks applied to the nerve. The muscle could then be thrown into a tetanus by a single impulse conducted physiologically past the subliminally stimulated zone of the nerve. Presumably, the threshold at the subliminally stimulated area was lowered sufficiently during the supernormal period following the single propagated impulse for the latent or subliminal stimulation to become effective. It set up, thus, a second impulse, which was again followed by a supernormal phase permitting a third response, and so on.

In the heart, as in Granit and Skoglund's ephapse,[6] a single response is apparently not ordinarily followed by intense enough supernormality to set up a new pacemaker, although of course this is precisely what does occur in bigeminy, and in some of the more active preparations of the "artificial synapse" described in an earlier report by Granit and Skoglund.[7] It is, however, known that "staircasing," that is, increase in the amplitude of the negative after-potential with repetitive firing, can occur to a limited degree in nerve, and is more pronounced, apparently, the shorter the interval between spike responses.[8,9,10] It is therefore possible that *two* closely paired responses may induce pacemaker activity in a favorable locus through the increment in supernormality evoked by the pairing. In theory, adequate "staircasing" of supernormality, might be expected at times to require more than two, and indeed several, responses, and in fact it has been observed that, especially in preparations that had been fibrillated and defibrillated several times, the sensitivity seemed to become reduced, and as many as three or four impulses were required to induce pacemaker response of the cooled area (Fig. 5).

The fate of such ectopic pacemakers depends on a number of factors. Gasser[8] has found that while supernormality "staircases" to an early maximum, the subnormality that accompanies the positive after-potential is truly cumulative; and in nerve preparations he has shown how spontaneous repetitive firing based on supernormality can be overwhelmed by the rising tide of subnormality which it engenders. This may well occur in the heart, and account for the cessation of a ventricular tachycardia as well as for the somewhat prolonged pause that succeeds it.

If, however, the "staircasing" of supernormality is progressive for more than a few beats, and if other factors are intense enough to maintain pace-

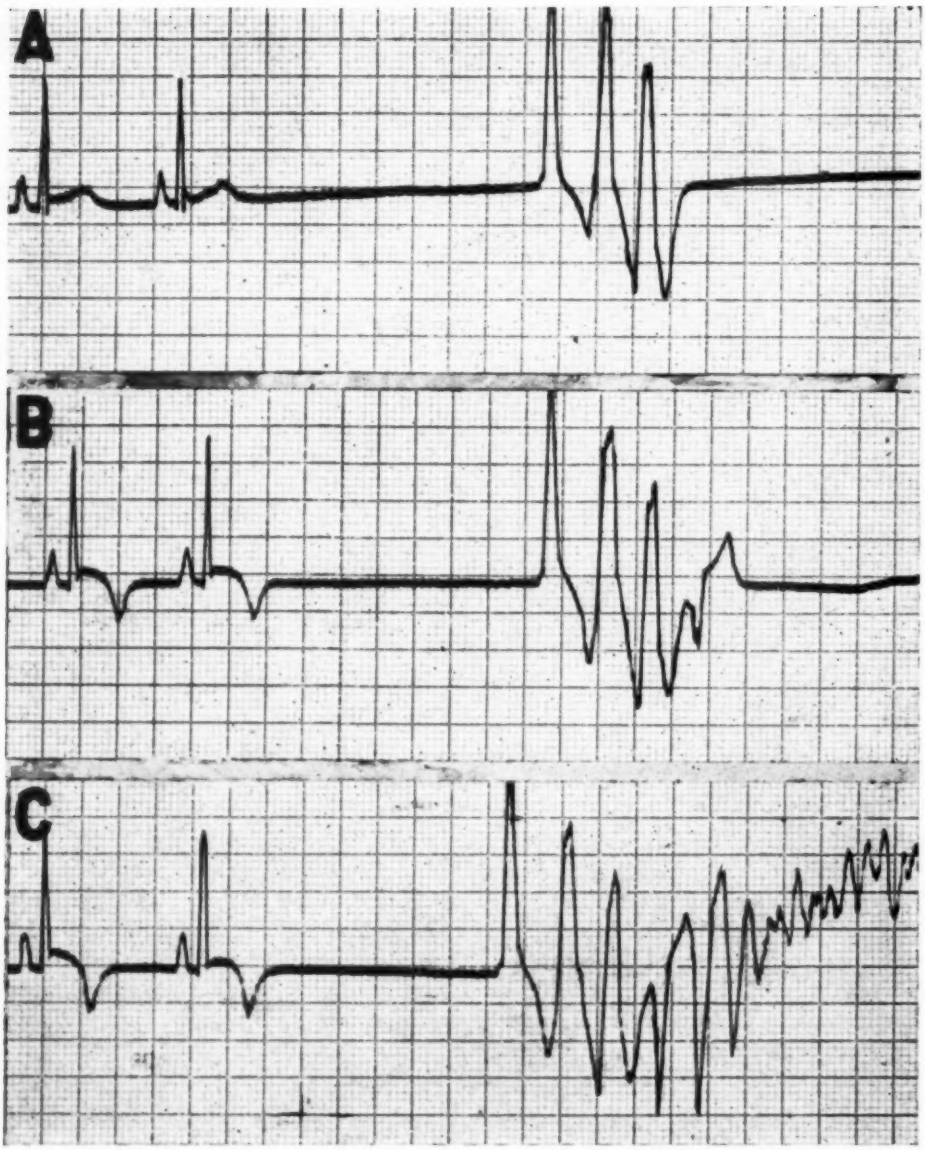


Fig. 5.—*A*, Three closely spaced responses to stimulation of the right base in a normal heart (upright T waves) arrested by the vagus. *B*, Early stage of cooling the left apex (inverted T waves). The three responses from stimulation at the right base are followed by a single spontaneous response from the cooled area. *C*, Later stage of cooling in the same experiment. At least three separate spontaneous responses from the cooled area are seen before fibrillation begins. Here not two, but three closely placed responses are required to induce pacemaker activity in the cooled area.

maker activity, the tachycardia accelerates in rate, because of the shortening of systole with increase in rate and the consequent earlier appearance of supernormality, and fibrillation supervenes. Evidence seems adequate that even in normal hearts an accelerating tachycardia produces regions of physiologic block while other avenues remain open, so that sooner or later an impulse takes a unidirectional course, leaving a route open by which it may return to set up fibrillation. Undoubtedly cooling creates, at the junction between cooled and normal tissue, regions of differing conductivity and differing rates of recovery, which would also facilitate the development of fibrillation. This may account for some instances when fibrillation seems to have begun almost immediately, with little tachysystolic interlude.

The rate of accommodation of many tissues is diminished by cooling, and this presumably also happens in the heart. This would provide an indispensable background for the development of repetitiveness. Accommodation may be defined as the process opposing the excitatory change brought about by a stimulus, and by some it is considered to be identical with cathodal depression.[12] Whatever its nature may be, its effect is to render the tissue unresponsive to a constant stimulus, at a rate characteristic of the tissue and its environmental conditions. The process may be so strongly developed that the tissue will respond but once at the commencement of a constant stimulus; thereafter the stimulus will be ineffective. This is the situation found, for instance, in mammalian motor nerve fibers. On the other hand, tissues that accommodate more slowly or less strongly are able to respond again after recovery from the refractory period left by the first response, and thus a longer or shorter series of repetitive discharges will follow the application of a constant stimulus.

It is known, too, that a cooled region becomes electronegative to normal tissues; this is shown by the large apparent injury currents that develop, reversibly, with local cooling of the mammalian heart,[11] and a similar influence of cold has been noted in other tissues.[6] These two factors provide, then, a constant stimulus, resembling electrotonus, and the reduced accommodation, which combine to permit repeated responses to take place to that constant stimulus, once the threshold has been lowered during the course of the supernormal period following the second of the paired induced responses.

This attempt to explain ectopic phenomena in the mammalian heart in terms of mechanisms observable in simpler excitable tissues such as vertebrate and even invertebrate nerve fibers, and so forth, justifiable as it is even on a priori grounds, and supported by the striking parallel between events at the cooled ephapse and the cooled zone of the mammalian heart, cannot be considered as more than a preliminary exploration of the possibilities, in keeping more with classical neurophysiologic doctrines of rhythmic response than with certain later studies. Invoking as it does the existence of a constant stimulus, eliciting rhythmic discharge because of absence of adequate accommodation to terminate responsiveness of the tissue to the constant stimulus, and spaced by the characteristics of the recovery cycle, it coincides with the account of rhythmic discharge of cut nerve fibers given by Adrian,[13] where the injury potential at the cut end serves as the constant stimulus, the explanation of dis-

charge in the optic nerve offered by Bernhard, Granit, and Skoglund,[14] according to which the slow retinal potentials provide a relatively constant stimulus, and many others.

The conditioning of rapid rhythmic discharge by supernormality has been commented on by Erlanger and Gasser,[12] and even in crustacean nerves Hodgkin[15] has confirmed the observation that nerves showing pronounced supernormality discharge at rapid and fairly fixed rates when stimulated by constant currents. Axons without significant supernormality discharge repetitively at frequencies that are generally slower and always more variable with change in stimulus intensity.

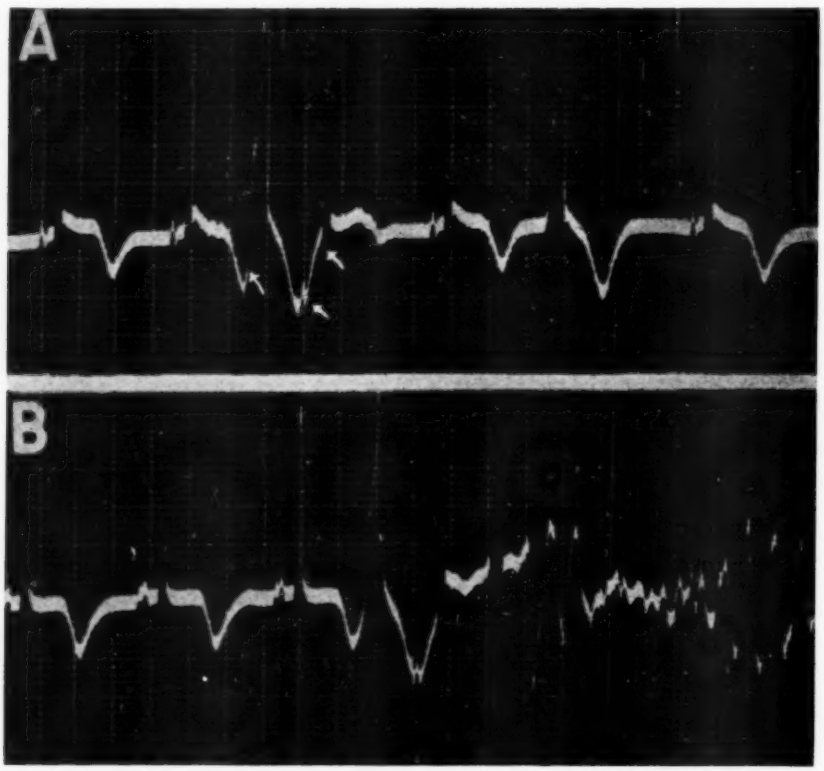


Fig. 6.—*A*, An interpolated extrasystole in early cooling. The arrows indicate, from left to right, (a) the beginning of the interpolated response, (b) the P wave of the subsequent supraventricular response, and (c) the subsequent normal response after a prolonged P-R interval showing an altered T wave. *B*, A later stage of cooling. Pacemaker response and subsequent ventricular fibrillation here follow not the induced extrasystole, but a normal supraventricular response, which, because of the interpolated extrasystole, has become the third of a series of closely placed impulses entering the cooled area.

Other factors may, however, be involved in the development and maintenance of repetitiveness at a pacemaker. In a variety of circumstances, as for instance at certain ephapses described by Granit and Skoglund,[7] a single response may be followed by fluctuations or oscillations of excitability in which

there is in effect rhythmic repetition of supernormal excitability, and this may be great enough to cause spontaneous discharges at the peaks of supernormality. This repetition of supernormal excitability after a response follows the same time course as do spontaneous fluctuations of excitability without previous stimulation, observable in stil more unstable tissues, such as nerve in calcium-free solution, and so forth, where again discharges may appear at periods of maximum excitability. The exact relationship of these periodic fluctuations in excitability, and the local electrical potentials with which they are associated, to the classical supernormal period and its accompanying negative after-potential is unclear, but they may well be found to represent one and the same metabolic process. Viewed in this light, the so-called "prepotentials," the presinus waves of Rijlant,[16] the prepotentials of Bozler[17] and others, and the oscillating local potentials of Harris and Moe[2] partake of the nature of after-potentials. This is in accord with Lorente de No's contention that the negative after-potential and catelectrotonus represent identical processes at the nerve membrane.[18]

Hodgkin has recently called attention to a factor he designates as "response-time," which in the crustacean nerve reflects the rate of development of the local potential that triggers the response of the tissue to a constant stimulus. Even in the rapid rhythms conditioned by supernormality this factor appears to be of importance, for the rate does not match the duration of the supernormal period following a single response. While the objection might be raised that the recovery cycle during rhythmic discharge is probably different from that following a single isolated response, and in fact varies with the rate, the work as a whole strengthens the view that factors other than the excitability cycle may contribute to condition the rate of periodic discharge at pacemakers. As Hodgkin points out, a large body of evidence emphasizes the variable nature of repetitive discharges.

SUMMARY

1. Local cooling of the dog's ventricle to 10° c. or below facilitates the development of ventricular fibrillation in response to a single threshold induction-shock stimulation of a noncooled region during early diastole.

2. Fibrillation develops as a terminal event after a short run of ventricular tachycardia, arising in the cooled area.

3. The fact that this series may stop spontaneously before fibrillation occurs indicates that it is in reality a series of separate impulses arising from pacemaker activity in the cooled area, and is not caused by circus motion.

4. Apparently the essential phenomenon of stimulation in the "vulnerable" part of the cycle is that it forces the potential pacemaker to respond at least twice in rapid succession.

5. It is suggested that this reaction presumably sets up spontaneous pacemaker activity in the cooled area by reason of "staircasing" of supernormality, which lowers the threshold sufficiently to produce one or more responses from the cooled area.

6. These responses develop at the cooled area because cooling has produced a potential difference between the cooled and adjacent areas, and they are maintained because the accommodation which normal tissues show to constant currents is reduced by the cooling.

REFERENCES

1. Moe, G. K., Harris, A. S., and Wiggers, C. J.: Analysis of the Initiation of Fibrillation by Electrographic Studies, Am. J. Physiol. **134**:473, 1941.
2. Harris, A. S., and Moe, G. K.: Idioventricular Rhythms and Fibrillation Induced at the Anode or the Cathode by Direct Currents of Long Duration, Am. J. Physiol. **136**:318, 1942.
3. Harris, A. S., and Rojas, A. G.: The Initiation of Ventricular Fibrillation Due to Coronary Occlusion, Exper. Med. & Surg. **1**:105, 1943.
4. De Boer, S.: On the Fibrillation of the Heart, J. Physiol. **54**:400, 1920-1921.
5. De Boer, S.: On Recurring Extra Systoles and Their Relation to Fibrillation, J. Physiol. **54**:410, 1920-1921.
6. Granit, R., and Skoglund, C. R.: The Effect of Temperature on the Artificial Synapse Formed by the Cut End of the Mammalian Nerve, J. Neurophysiol. **8**:211, 1945.
7. Granit, R., and Skoglund, C. R.: Facilitation, Inhibition, and Depression at the "Artificial Synapse" Formed by the Cut End of a Mammalian Nerve, J. Physiol. **103**:435 1944-1945.
8. Gasser, H. S.: Changes in Nerve-Potentials Produced by Rapidly Repeated Stimuli and Their Relation to the Responsiveness of Nerve to Stimulation, Am. J. Physiol. **111**:35, 1935.
9. Gasser, H. S., and Grundfest, H.: Action and Excitability in Mammalian A Fibers, Am. J. Physiol. **117**:113, 1936.
10. Gasser, H. S.: Recruitment of Nerve Fibers, Am. J. Physiol. **121**:193, 1938.
11. Personal observation.
12. Erlanger, J., and Gasser, H. S.: Electrical Signs of Nervous Activity, Philadelphia, 1937, University Press.
13. Adrian, E. D.: Effects of Injury on Mammalian Nerve Fibers, Proc. Roy. Soc. London **106B**:596, 1930.
14. Bernhard, C. G., Granit, R., and Skoglund, C. R.: The Breakdown of Accommodation—Nerve As a Model Sense-Organ, J. Neurophysiol. **5**:55, 1942.
15. Hodgkin, A. L.: The Local Electric Changes Associated With Repetitive Action in a Non-medullated Axon, J. Physiol. **107**:165, 1948.
16. Rijlant, P.: La conduction dans le coeur du mammifere, Arch. Internat. de Physiol. **33**:325, 1930.
17. Bozler, E.: Initiation of Impulses in Cardiac Muscle, Am. J. Physiol. **138**:273, 1942.
18. Lorente De No, R.: A Study of Nerve Physiology, New York, 1947, Laboratories of the Rockefeller Institute for Medical Research.

PATHOLOGY OF THE INTRAPULMONARY ARTERIES AND ARTERIOLES IN COARCTATION OF THE AORTA ASSOCIATED WITH PATENT DUCTUS ARTERIOSUS

JESSE E. EDWARDS, M.D., JOHN M. DOUGLAS, M.D., HOWARD B. BURCHELL, M.D., AND NORMAN A. CHRISTENSEN, M.D.

ROCHESTER, MINN.

ABOUT a year ago three of us took part in the study and later in the report of a case of patent ductus arteriosus wherein there were occlusive pulmonary vascular lesions and hypertrophy of the right ventricle.[1] The left ventricle was of normal size. The evidence supported a concept that the right ventricle had functioned as a systemic ventricle; that at times, at least, it had forced blood into the descending aorta. Our interest in the subject of the systemic right ventricle was further enhanced by the subsequent study of yet another case (Case 4 of this paper) in which the right ventricle seemed to have supplied blood to the descending aorta through a patent ductus arteriosus. In this case there had been a coarctation of the aorta proximal to the aortic mouth of a patent ductus arteriosus. There were changes in the intrapulmonary arteries and arterioles which narrowed the lumina of these vessels and so seemed to have caused an increased resistance to pulmonary blood flow.

Because the pulmonary vascular lesions in this case seemed to form an integral part of the circulatory phenomenon wherein the right ventricle assumed a systemic function, it seemed pertinent to make a study of the pulmonary vessels in three other cases of aortic coarctation associated with patent ductus arteriosus, for which material was in our pathologic files. This communication is a report of these three cases as well as of the first case of coarctation and patent ductus arteriosus mentioned. Particular reference will be made to the microscopic changes of the intrapulmonary vessels.

MATERIALS AND METHODS

Four cases formed the basis for this pathologic study. In each patient the gross specimens of the heart and great vessels had been saved and were available for restudy. A rib had been saved from each of two of the patients. In one patient one whole lung had been preserved and in another both lungs were available. In all patients, blocks of lung had been saved in fixative. From these and from the available gross specimens of lung, additional paraffin

From the Division of Medicine and the Section on Pathologic Anatomy, Mayo Clinic, Rochester, Minn.

Read before the Twenty-first Annual Meeting of The American Heart Association, Chicago, Ill., June 19, 1948.

blocks and sections were prepared. The original sections and the paraffin blocks from which they had been prepared were also present. From these blocks additional sections were cut and specially stained sections were made.

From each paraffin block that had been saved from the time of the original study of the respective case and from each of the paraffin blocks that were prepared additionally during this study, a section was stained with hematoxylin and eosin stain and another with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. Mallory's phosphotungstic acid hematoxylin stain and a modification of Mallory's aniline blue connective tissue stain were employed, additionally, on a few of the sections.

In addition to a qualitative study of the changes in the pulmonary arteries and arterioles, measurements were made on twenty to forty-five pulmonary arterioles from each patient. Like measurements were made on controls which were taken from normal lungs of ten individuals corresponding in respective a e groups to those of the four patients which form the basis of this study. One class of arterioles measured from 50 to 99 microns in external diameter; the other, from 100 to 200 microns. The vessels measured were ones that had been cut at right angles to their long axes.

A few arterioles with maximal changes which occluded their lumina were avoided in performing the measurements. The arterioles were measured according to the following method: Two measurements of the external diameter, adventitia included, one at a right angle to the other, were made and from these the average external diameter was calculated.

Two measurements of the diameter of the lumen were made, one at a right angle to the other, and from these the average luminal diameter was determined. From the determinations each of the external diameter and the luminal diameter the ratio of the luminal diameter to external diameter was calculated.

REPORT OF CASES

CASE 1.—*Clinical History*: A 15-year-old girl was first seen at the Mayo Clinic when she was 11 years old because of progressive scoliosis. She had always had a normal tolerance to exercise.

On the first admission there was a harsh systolic murmur which was heard loudest at the cardiac apex and over the pulmonary area. In an arm, the blood pressure was 130/82. The eye grounds were normal.

For the treatment of the scoliosis, a spinal fusion by means of a bone graft was carried out on Dec. 29, 1941. The convalescence was uneventful.

The patient returned to the clinic during the fall of 1945 because of continued spinal deformity. The graft made on the first admission was solidly united, but there seemed to be progression of the curvature above and below the graft. The auscultatory signs of the heart were the same as on the first admission. In addition, there was marked accentuation of the pulmonary second sound. The blood pressure was 100/80. On Oct. 25, 1945, further bone grafts were placed in the spinal column.

Postoperatively there was slight dyspnea and slight persistent cyanosis of the left hand. On the sixth postoperative day, without warning signs, the patient lost consciousness and died after being deeply comatose for approximately ten minutes.

On both visits of the patient to the clinic the roentgenograms of the thorax showed evidence of slight cardiac enlargement. The electrocardiograms revealed right axis deviation. On the first visit there were 14.4 Gm. of hemoglobin per 100 c.c. of blood; the value was 13.3 Gm. on the second visit.

The history had been somewhat difficult to obtain as neither the patient nor her parents spoke English. After the patient's death, a physician who spoke their language fluently obtained from the parents the history that for some years there had been intermittent slight cyanosis of the left hand.

Necropsy Findings.—

Gross Observations: The heart, the great vessels, and the vessels of the lungs were of greatest interest pathologically. The great vessels showed two malformations: a patent ductus arteriosus, measuring 0.6 cm. in length and 0.4 cm. in luminal diameter, and coarctation of the aorta. The aortic mouth of the ductus arteriosus lay 3.0 mm. proximal to the zone of aortic coarctation (Fig. 1,*a* and *b*). The appearance of the aorta at the zone of narrowing was typical of that seen in coarctation in that the superior, anterior, and posterior aspects of the vessel showed an external concavity which corresponded in location to a diaphragm-like membrane lying across the lumen of the aorta. In the lower aspect of this membrane there was an opening which admitted only a fine probe. It measured less than 1.0 mm. in diameter and it constituted all of the aortic lumen at the site of coarctation. The aortic mouths of the intercostal arteries were dilated, bearing evidence that a collateral system of arteries existed to bypass the zone of narrowing of the aortic lumen. The entire aorta was thin walled and the caliber of the abdominal aorta was narrow. The usual three arteries arose from the aortic arch.

It was of interest that there was no intimal patch in the left pulmonary artery opposite the mouth of the patent ductus arteriosus, a lesion which is common in the usual case of uncomplicated patent ductus arteriosus. Instead, the aortic intima proximal to the coarctation, in relation to the aortic mouth of the ductus arteriosus, was gray and thickened, as though by the presence of an increased amount of fibrous tissue. The pulmonary trunk and its major branches were unusually thick walled. Whereas the wall of the ascending aorta measured 1.0 mm. in thickness, that of the pulmonary trunk measured 1.8 millimeters.

The heart was somewhat enlarged, weighing 310 grams. The weight of a normal heart of a 15-year-old girl is approximately 250 grams. The condition of the right ventricle constituted the chief cause of the enlargement. It occupied an unusually large proportion of the outer surface of the ventricular part of the heart and its wall was considerably hypertrophied, measuring 1.5 cm. in average thickness. The left ventricular wall was only slightly hypertrophied; it was 1.3 cm. thick (Fig. 1,*a* and *b*). The size of the chambers of the atria and of the left ventricle were within normal limits. The right ventricular chamber was moderately dilated.

The mural endocardium of the left-sided chambers and of the right atrium was diffusely thickened to a slight degree; their surfaces were opaque and gray.

The foramen ovale was probe patent. The ventricular septum was closed. The aortic valve was congenitally bicuspid. No anomalies were present in the other valves or great veins.

The pulmonary orifice measured 5.7 cm. in circumference; the aortic, 4.4 centimeters. The lungs, save for absence of the right middle lobe, were not remarkable in gross appearance. There was no atherosclerosis of the larger pulmonary arteries. The remaining viscera were within normal limits. A marked scoliosis to the right involved the vertebral column from the level of the third thoracic to the fourth lumbar vertebra.

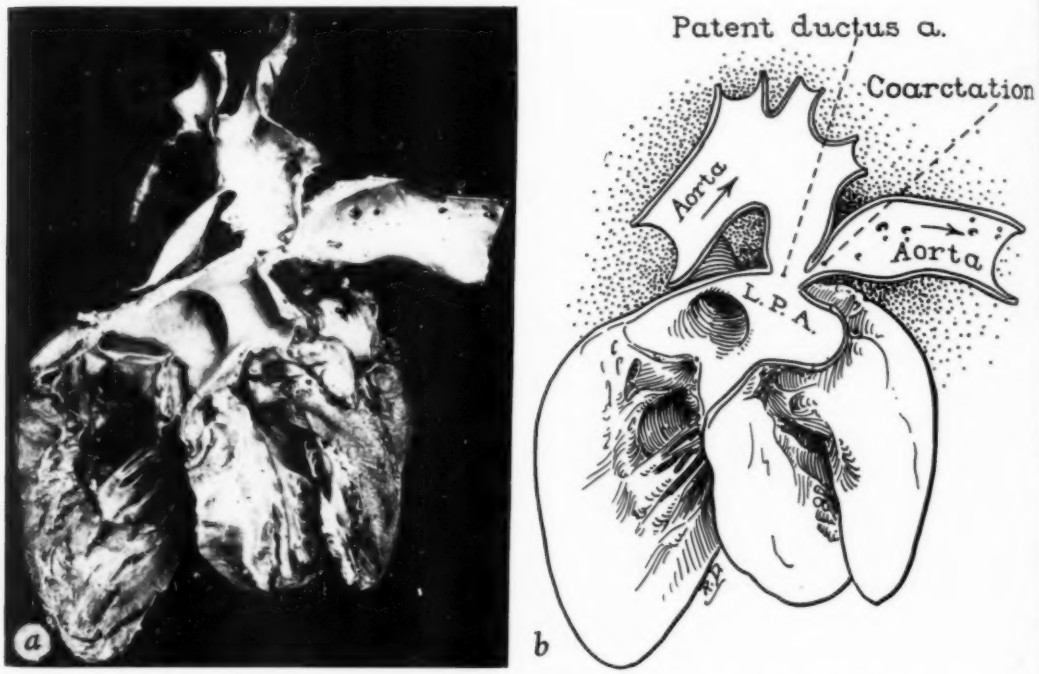


Fig. 1.—Case 1. *a*, The heart and great vessels. Each ventricular wall and chamber is exposed. The pulmonary trunk and the left pulmonary artery have been opened, as has the aorta, except at the zone of the aortic coarctation. The probe lies in the aortic lumen at the level of the coarctation. The right ventricular wall is greatly hypertrophied, exceeding somewhat the thickness of the left ventricular wall, which is slightly hypertrophied. A patent ductus arteriosus joins the lumen of the left pulmonary artery and that of the aorta proximal to the coarctation. In the exposed descending aorta the dilated ostia of the aortic intercostal arteries are shown. The intima of the left pulmonary artery is smooth. A "jet" lesion is lacking in the lower aspect of this vessel, a lesion often seen in uncomplicated cases of patent ductus arteriosus and present in Case 2 (Fig. 2, *a* and *b*). *b*, Diagrammatic sketch of anatomic features illustrated in *a*. *L. P. A.* means left pulmonary artery.

Since the changes in the intrapulmonary vessels were essentially similar in the first two cases, they will be described after the report of Case 2.

CASE 2.*—*Clinical History*: A 22-year-old man came to the clinic on Dec. 15, 1930, because of a mediastinal tumor. In the five-year period during which the tumor was known to

*This case report is republished with permission from Lemon, W. S.: Case of Congenital Abnormality of the Heart, Coarctation of Aorta and Neurofibroma of Mediastinum, Tr. A. Am. Physicians 46:340, 1931.

be present it had not changed in size, shape, or density, nor had it produced dyspnea. Tolerance to exercise had been normal. Several months before coming to the clinic the patient had begun to have pain in the thorax associated with discomfort when using the left arm. There was nothing in the patient's history to suggest a cardiac or circulatory defect.

Physical examination revealed that the lips were cyanotic to a slight degree. There was a coarse thrill over the sternum at the level of the second intercostal space and the thrill could be felt some distance from this area of maximal intensity. A systolic murmur corresponded to the distribution of the thrill. The cervical vessels pulsated strongly. Pulsations could be felt over the thorax, but the pulsations of the abdominal aorta could not be felt. In an arm the blood pressure was 185/80. The blood pressure in the legs could not be recorded. Electrocardiographic study included only the three standard leads. The results may best be interpreted as indicating left bundle branch block.

The roentgenograms of the thorax revealed a dense circumscribed tumor in the left upper portion of the thoracic cavity. The tumor appeared to displace the left lung downward and the trachea, esophagus, and heart to the right. Several of the ribs showed notching consistent with that seen in coarctation of the aorta, and this diagnosis was made. Surgical exploration for the thoracic tumor was carried out and the tumor which occupied the posterior mediastinum was removed in its entirety. It was found to be a neurofibroma. The patient's immediate postoperative reaction was good, but he gradually failed and died of bronchopneumonia six days postoperatively on Dec. 26, 1930.

Necropsy Findings.—

Gross Observations: The vascular malformations in this case were virtually identical to those in Case 1. There was a patent ductus arteriosus measuring approximately 3.0 mm. in length and 5.0 mm. in diameter, which opened into the aorta just proximal to a point at which aortic coarctation existed. At the zone of coarctation, the aortic lumen measured 2.0 mm. in diameter. In contrast to the finding in the first case, the lower aspect of the origin of the left pulmonary artery and the adjacent pulmonary trunk showed a raised, gray, corrugated intimal patch which measured 1.5 by 1.0 centimeter. It rose somewhat less than 1.0 mm. above the general level of the intimal surface. Microscopically the lesion was characterized by intimal thickening with collagen, fibroblasts, and cells resembling smooth muscle cells (Fig. 2,*a* and *b*). It is considered a "jet" lesion representing a reaction to the trauma of a jet of blood directed through the patent ductus arteriosus into the pulmonary arterial system. The usual arterial branches arose from the aortic arch and were wider than normal. As in the first case, the aortic mouths of the intercostal arteries were wide and were considered to represent functioning collateral channels by-passing the aortic coarctation. This was supported by some widening and erosion of the costal groove of the rib which had been removed surgically. This change is seen in cases of coarctation in which there is a well-developed collateral system.

The wall of the ascending aorta was of usual thickness, measuring about 1.8 millimeters. The wall of the pulmonary trunk measured 1.0 mm. in thickness.

The weight of the heart was 626 grams, the expected normal being 275 grams. The enlargement resulted from hypertrophy of each ventricle but particularly the left. The right ventricular wall measured 0.9 cm. in average thickness; the left, 1.8 centimeters. There was moderate dilatation of both

ventricular chambers. The mural endocardium of the left atrium was somewhat thickened, gray, and opaque. The intracardiac septa were intact and there were no anomalies of the great veins. The aortic valve was congenitally bicuspid; its orifice measured 5.0 cm. in circumference. The pulmonary orifice measured 7.0 cm. in circumference. Inferior to the commissure between the right and anterior leaflets of the pulmonary valve there was a small, gray elevation, measuring about 0.3 cm. in diameter, that involved the endocardium of the right ventricle. This resembled an ill-defined endocardial pocket, suggesting morphologically that a degree of pulmonary valvular insufficiency had existed at some period during the life of the patient.

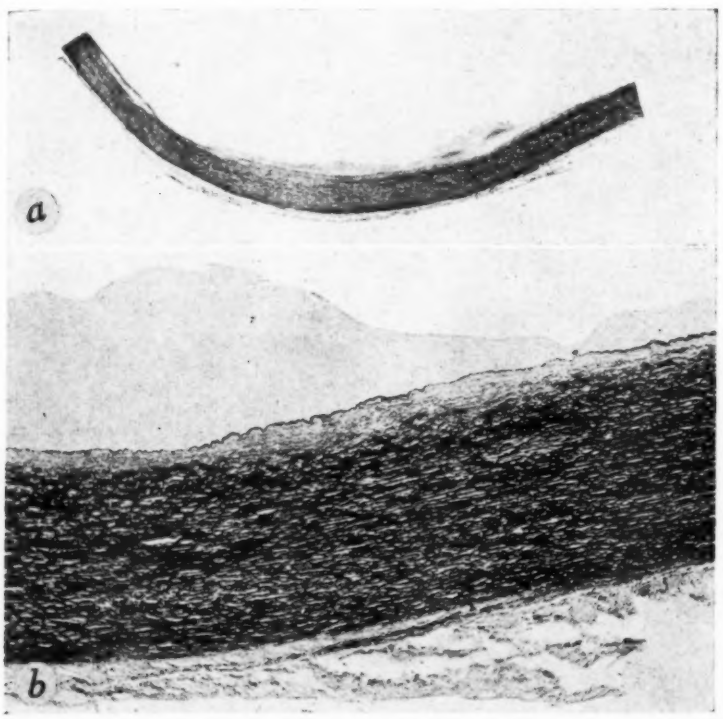


Fig. 2.—Case 2. Sections stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, "Jet" lesion in the left pulmonary artery. Normal intima is shown at the edges of the photograph. The intervening intima is thickened by collagen and cells, some of the latter being fibroblasts; others appear as smooth muscle cells. The lesion is considered a reaction to the trauma caused by a jet of blood entering the left pulmonary artery and traumatizing the intima (×4½). *b*, A portion of the "jet" lesion portrayed in *a* (×25).

Grossly the lungs were not particularly remarkable. The abdominal viscera showed minor congenital anomalies in the form of unilateral partial duplication of the ureter and a diverticulum of the duodenum.

Microscopic Observations in Cases 1 and 2.—The microscopic changes in the pulmonary vessels in Cases 1 and 2 were essentially alike and will be described

together. The small intrapulmonary arteries showed medial muscular hypertrophy and, frequently, unusually heavy internal elastic laminae were present (Figs. 3,*a* and *b* and 4,*a* to *d*). In some arteries this elastic layer was fragmented and reduplicated, fibers of elastic tissue being intermingled with the smooth muscle of the media (Fig. 4,*c* and *d*). Intimal fibrous thickening in which the fibroblasts and collagen were arranged in concentric layers was a frequent finding (Figs. 4,*a* to *d* and 5,*a* to *c*). In many instances the intimal tissues caused only a slight degree of luminal narrowing. In other vessels they were responsible for considerable narrowing to complete closure of the lumen (Fig. 6,*a*). In Case 2 hyalinization of the media alone was occasionally observed (Fig. 5,*b*), while other arteries in this case showed hyalinization involving the thickened intima as well as the media (Figs. 5,*c* and 6,*a*). Hyalinization of arterial walls was not observed in Case 1. In both cases, in addition to the lesions described, some arteries contained thrombi of varying ages. These were numerous in the first case. In some arteries the thrombi were fresh and organization had just begun (Fig. 6,*b*). In others the lumen was represented by a plexiform arrangement of capillaries lying in dense fibrous tissue, a picture consistent with recanalized thrombi (Fig. 6,*c*). In such instances the effective channel through the vessel was obviously narrowed. In rare arteries in Case 1, at the junction of the media and intima, there were endothelial-lined vessels

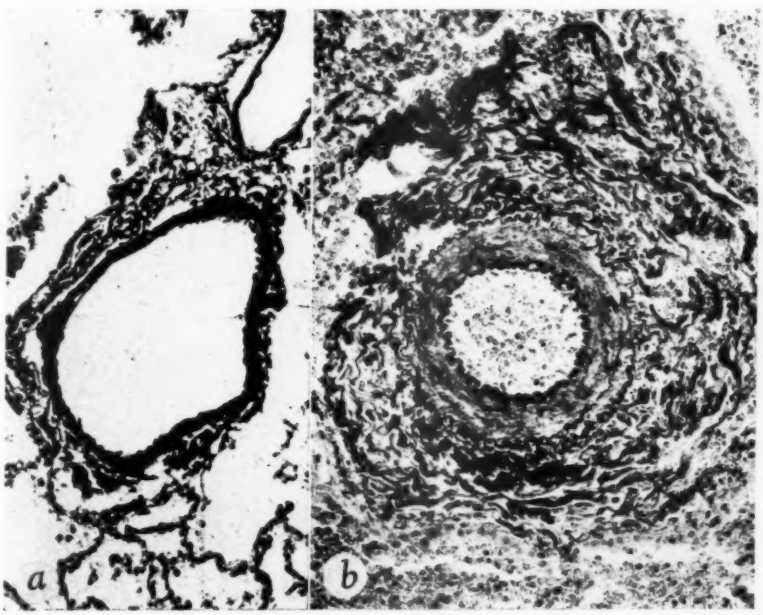


Fig. 3.—Sections stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, Control for comparison with Fig. 3,*b*. Normal intrapulmonary artery from a normal lung of a 17-year-old girl (×145). *b*, Case 2. Intrapulmonary artery showing medial muscular hypertrophy and fibrous thickening of the adventitia. The internal elastic lamina is thick. There is no intimal thickening in this artery. The lumen is relatively narrow for the size of the vessel. Compare with control, Fig. 3,*a* (×145).

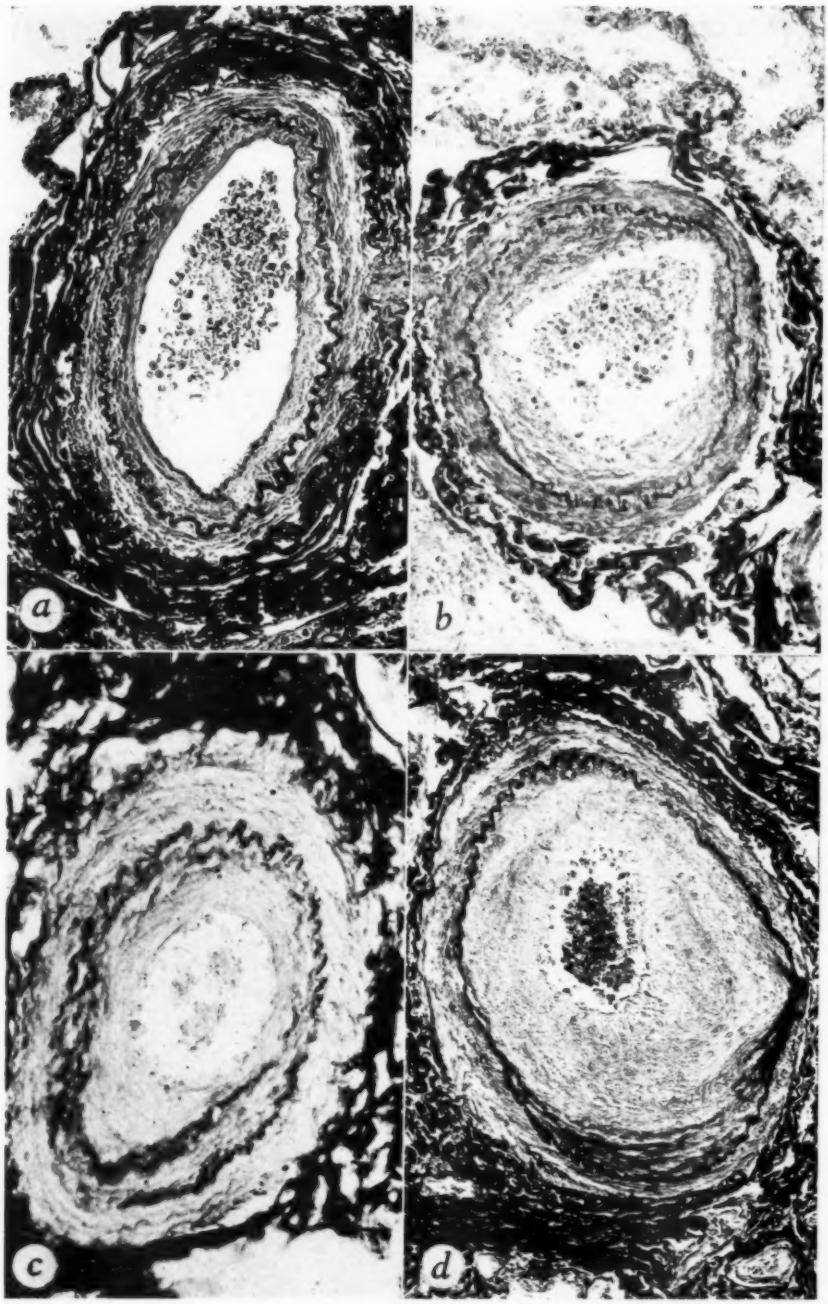


Fig. 4.—Sections of intrapulmonary arteries stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, Case 1. Prominence of internal elastic lamina. Fibrous thickening of intima. Adventitial fibrosis. The lumen is narrow for the size of the vessel (×185). *b*, Case 2. Prominence of the internal elastic lamina. Intimal fibrous thickening (×185). *c*, Case 1. Fragmentation of internal elastic lamina. Shreds of elastic tissue are intermingled with the elements of the hypertrophied media. Intimal fibrosis. Narrowing of the lumen (×225). *d*, Case 1. Prominence and focal reduplication of the internal elastic lamina. Marked intimal thickening by fibrous tissue causing an extreme degree of luminal narrowing. Adventitial fibrosis (×130).

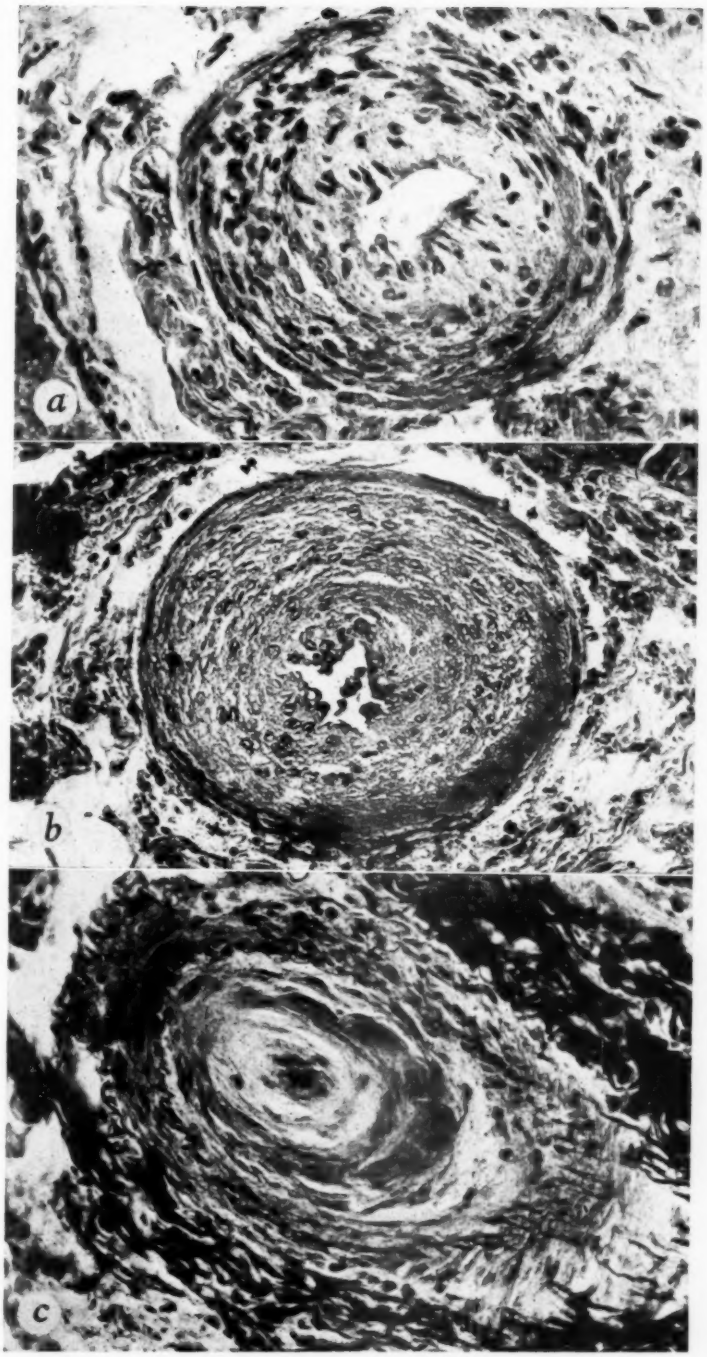


Fig. 5.—Small intrapulmonary arteries. *a*, Case 2. The media is hypertrophic and the intima shows considerable fibrous thickening. These changes cause considerable narrowing of the lumen and thickening of the wall (hematoxylin and eosin, ×315). *b*, Case 2. Luminal narrowing caused by marked concentric fibrous thickening of the wall, particularly the intima. Focal hyalinization of the media (hematoxylin and eosin, ×260). *c*, Case 2. The lumen is virtually occluded by fibrous thickening of the intima. There is hyalinization of the intimal tissue. The internal elastic lamina is fragmented (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, ×330).

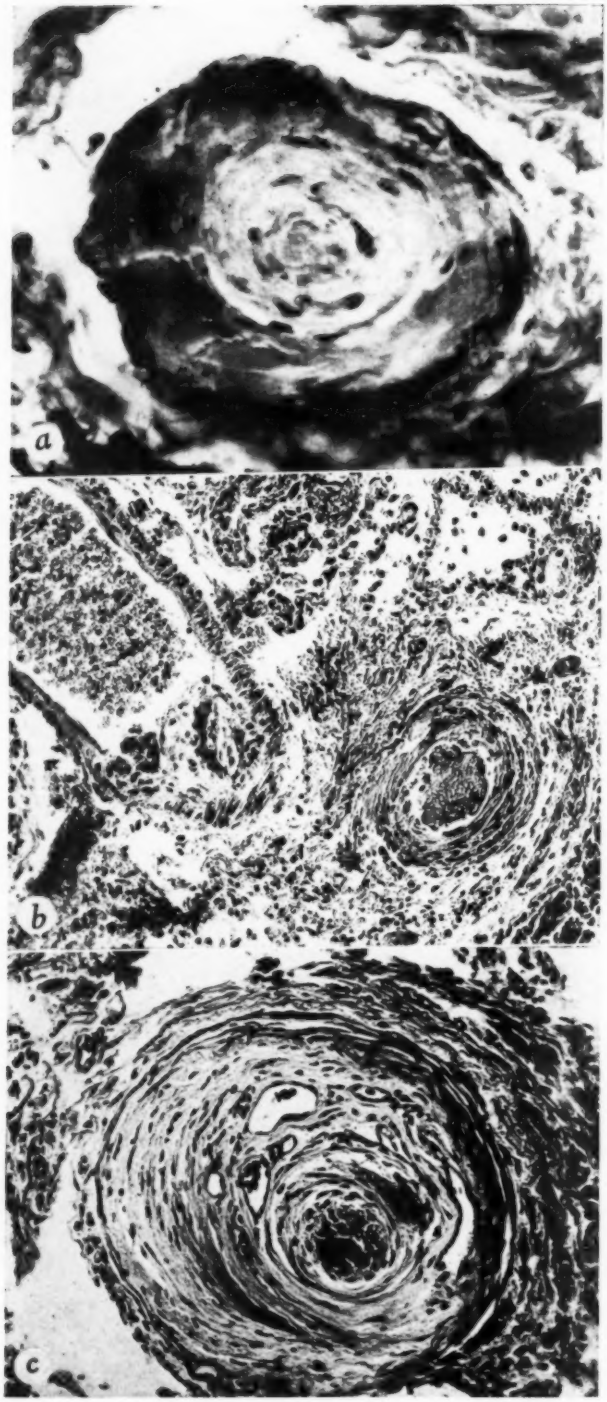


Fig. 6.—Sections of intrapulmonary arteries stained with hematoxylin and eosin. *a*, Case 2. The lumen is occluded by fibrous intimal thickening. There is considerable hyalinization of the intimal and medial layers (×570). *b*, Case 2. The lumen of the artery shown in cross section is plugged by a fresh thrombus. A portion of an artery cut longitudinally is shown. Its lumen contains a mural thrombus which is undergoing organization. The vessel shown in cross section exhibits medial hypertrophy (×170). *c*, Case 1. The arterial lumen is replaced by a matrix of connective tissue that contains capillaries. The picture is that of an organized and recanalized thrombus (×200).

containing blood. The intramural vessels could have represented recanalized thrombi or healed small dissecting aneurysms.

In Cases 1 and 2, while the alterations in structure of the intrapulmonary arteries were disseminated and readily evident, many of the arterioles showed only moderate degrees of mural thickening. Rare arterioles showed hyalinization, either diffuse or focal, of their walls.

A few arterioles showed marked medial hypertrophy (Fig. 7,*a* and *b*), and adventitial thickening was present in others. A rare vessel of this caliber showed concentric fibrous thickening of its intima, a process which resulted in a considerable degree of luminal narrowing (Fig. 7,*c* and *d*). These changes were not numerous, however. None of the arterial and arteriolar lesions were associated with deposits of lipoid-filled macrophages. There were moderate degrees of capillary engorgement, but otherwise the capillaries showed no morphologic change. The veins were not remarkable.

Quantitative measurements, recorded in Table I, of arterioles in Cases 1 and 2 revealed that the ratio of luminal diameter to external diameter was reduced as compared to that based on normal controls from individuals of comparable ages. In control arterioles measuring from 50 to 99 microns in external diameter, the lumen comprised 70 per cent of this diameter, while in Case 1 the lumen constituted but 58 per cent of the total diameter of arterioles with similar external diameters. In Case 2 the lumen constituted 53 per cent of the total diameter of arterioles of similar order. Similarly, arterioles measuring from 100 to 200 microns in external diameter showed a reduction in the expected diameters of their lumina. Whereas in the controls the lumina constituted 75 per cent of the total diameter of the arterioles, in Case 1 the lumen comprised 62 per cent and in Case 2 the lumen comprised 58 per cent of the total diameter

TABLE I. COMPARISON OF DIAMETERS OF ARTERIOLAR LUMINA WITH THOSE OF NORMAL ARTERIOLES

EXTERNAL DIAMETER FROM 50 TO 99 MICRONS				EXTERNAL DIAMETER FROM 100 TO 200 MICRONS			
CASE	RATIO OF LUMEN TO EXTERNAL DIAMETER		WIDTH OF LUMEN (PER CENT OF NORMAL)	CASE	RATIO OF LUMEN TO EXTERNAL DIAMETER		WIDTH OF LUMEN (PER CENT OF NORMAL)
	CONTROL	CASE			CONTROL	CASE	
1	.70	.58	83	1	.75	.62	83
2	.70	.53	76	2	.75	.58	77
3	.69	.39	57	3	.75	.40	53
4	.69	.44	64	4	.75	.44	59

Average width of lumina of arterioles of all diameters measured, as compared with average of controls of similar diameters from comparable age groups:

Cases 1 and 2: 80 per cent of control diameter
Cases 3 and 4: 58 per cent of control diameter

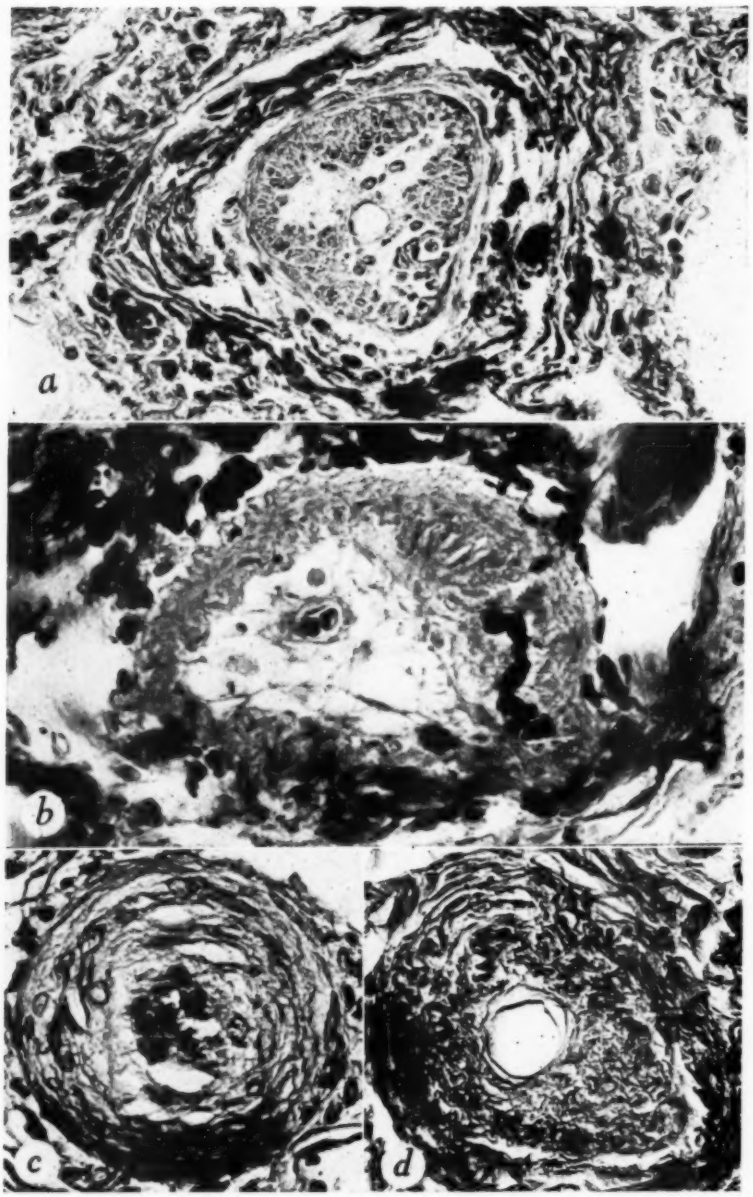


Fig. 7.—Pulmonary arterioles. *a*, Case 1. Medial hypertrophy causing considerable narrowing of the lumen. Adventitial fibrosis (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, ×340). *b*, Case 2. The media shows considerable hypertrophy. The lumen is replaced by a recanalized thrombus (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, ×515). *c*, Case 1. The lumen is greatly narrowed by concentric fibroblastic proliferation of the intima (hematoxylin and eosin, ×365). *d*, Case 1. The lumen is narrowed by intimal proliferation of fibrous tissue. Thickening of the adventitial coat. The internal elastic lamina is prominent in some places and interrupted in others (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, ×365).

of the arterioles. Thus in Case 2 the arterioles with external diameters ranging from 50 to 99 microns showed lumina only 76 per cent as wide as expected and in the same case the lumina of arterioles measuring 100 to 200 microns in external diameter were 77 per cent as wide as the lumina of control arterioles.

Similarly in Case 1 the lumina of the smaller and the larger classes of arterioles were only 83 per cent as wide as the expected normal. If the two classes of arterioles in Cases 1 and 2 are compared with normal arterioles of similar sizes, it is observed that the diameter of the average lumen in these two cases is only 80 per cent as wide as that of normal arterioles.

CASE 3.*—*Clinical History*: A 23-month-old female infant was admitted to the hospital on June 2, 1923, because of massive generalized edema. Because of respiratory difficulty artificial respiration had been necessary immediately after birth. Her physical development had been retarded. During the five months prior to admission to the hospital she had had fainting spells. No cyanosis had been observed until shortly before admission.

Physical examination showed a poorly nourished child measuring 33¾ inches (85.7 cm.) in height. She weighed 23 pounds (10.4 kilograms). There was marked dyspnea and generalized cyanosis. The systolic blood pressure, presumably taken in an arm, was recorded as 90, expressed in millimeters of mercury. The diastolic pressure could not be definitely ascertained.

The heart was enormously enlarged and there was a blowing systolic murmur over the apex. A soft blowing diastolic murmur was heard to the right of the sternum. There were signs of pulmonary congestion as well as massive anasarca and enlargement of the liver.

The infant's condition deteriorated progressively and she died on the sixth day in the hospital.

Necropsy Findings.—

Gross Observations: Examination of the great vessels revealed a coarctation of the aorta associated with a patent ductus arteriosus. In contrast to the lesion in Cases 1 and 2, the coarctation in this case lay proximal to the aortic mouth of the ductus arteriosus (Fig. 8,*a*). The diameter of the aortic lumen at the zone of coarctation measured 2.0 millimeters. The luminal diameter of the ductus arteriosus measured 2.0 mm. (Fig. 8,*b*). The aortic mouths of the intercostal arteries were of normal caliber. Since no prominent collateral system of arteries existed, it was interpreted that the aorta below the coarctation had received part of its blood from the aortic arch through the site of aortic narrowing and part through the patent ductus arteriosus from the left pulmonary artery and, ultimately, the right ventricle. As an additional anomaly, the left vertebral artery arose from the aortic arch.

Examination of the heart revealed tremendous enlargement of the right ventricle and a small defect of the membranous portion of the ventricular septum. The heart was enormously increased in weight, weighing 215 grams. The normal cardiac weight for a 23-month-old female infant is 50 grams. The cardiac enlargement resulted mainly from the size of the right ventricle. This chamber constituted the major part of the ventricular portion of the heart, to

*This case report is republished with permission from Blackford, L. M.: Coarctation of Aorta, Arch. Int. Med. 41:702, 1928.

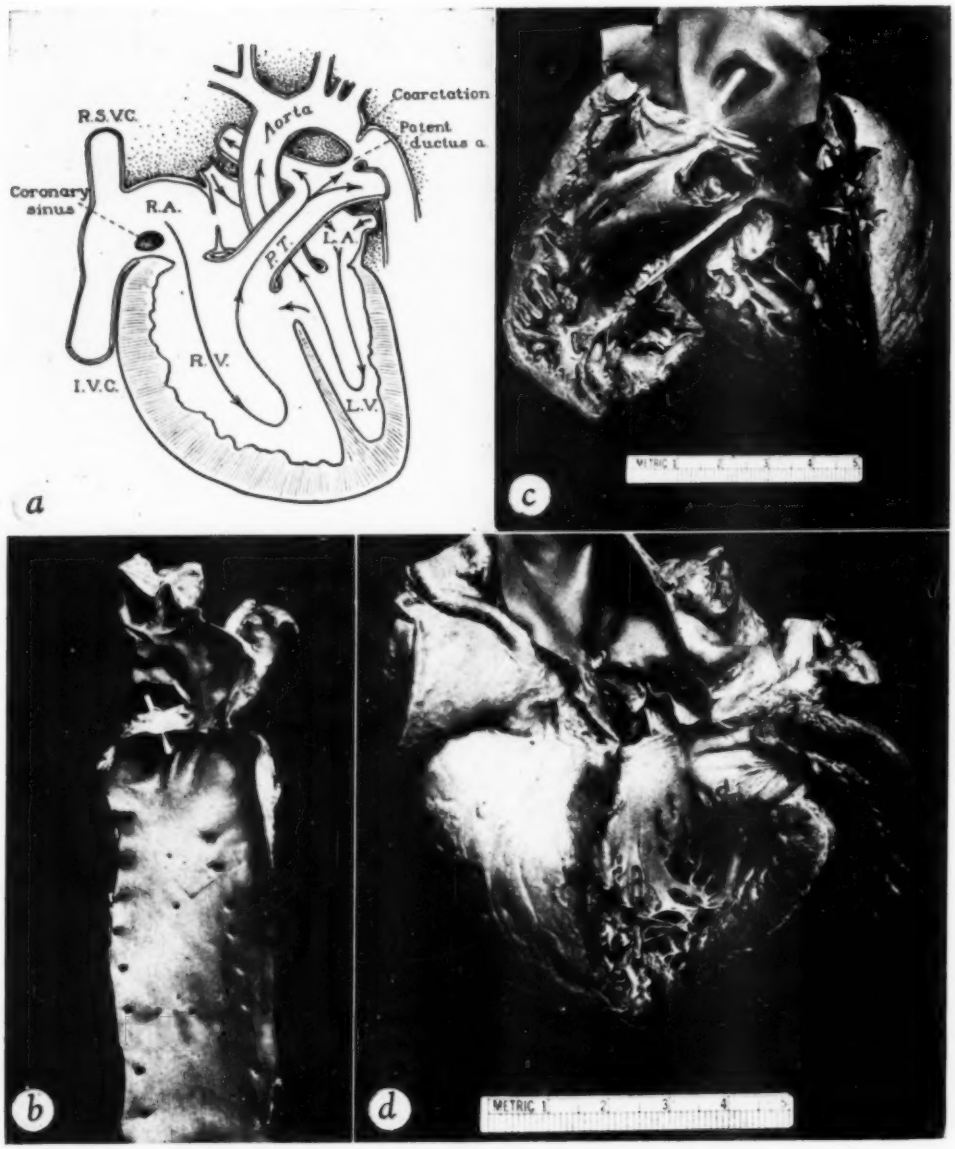


Fig. 8.—Case 3. *a*, The heart and great vessels. There is coarctation of the aorta proximal to the aortic entrance of a patent ductus arteriosus. There is a defect of the membranous portion of the ventricular septum. The right ventricular chamber is enlarged and its wall is hypertrophic. The left vertebral artery arises from the aortic arch. *b*, The thoracic aorta. There is a zone of coarctation proximal to the entrance of a patent ductus arteriosus (probe). *c*, The right ventricle is considerably enlarged. Compare with the left ventricle, *d*. There is an artefact in the subpulmonary region. *d*, The left ventricle. The size of the chamber is within normal limits. The wall is somewhat hypertrophied. The exterior of the right ventricle is seen in the background.

such a degree that the left ventricle, which was essentially of normal size or slightly enlarged, appeared merely as an appendage of the right ventricle. The height of the left ventricular chamber, as measured from the apex of that chamber to the line of attachment of the aortic leaflets, was 4.5 centimeters. From the line of attachment of the pulmonary cusps to the apex of the right ventricle the distance was likewise 4.5 centimeters. The right ventricular chamber was considerably wider than the left. It extended 4.0 cm. to the right of the right surface of the ventricular septum, while the left ventricular cavity extended but 1.3 cm. to the left of the left surface of the ventricular septum. The left ventricular wall measured 0.8 cm. in thickness; the right, from 0.8 to 1.4 cm. (Fig. 8,*c* and *d*). A defect measuring 0.5 by 0.5 cm. involved the membranous portion of the ventricular septum (Fig. 9). Anatomic patency of the foramen ovale was present, the opening measuring 0.7 by 0.2 centimeter. The left atrium was of normal size, while the right atrium was dilated. The pulmonary veins drained into the left atrium. There was a persistent left superior vena cava which entered the coronary sinus at the left border of the heart. The aortic valve was congenitally bicuspid (Fig. 9). The remaining valves were normal. The pulmonary orifice measured 4.8 cm. in circumference; the aortic, 3.0 cm.; the mitral, 4.2 cm.; and the tricuspid, 7.0 centimeters. The lungs were not remarkable in gross appearance.

Fig. 9.—Case 3. Interior of the left ventricle and the aorta. There is a defect in the membranous portion of the ventricular septum. The aortic valve is bicuspid.

In many ways the microscopic appearance of the intrapulmonary arteries and arterioles in this case were identical with those in Case 4. Consequently, the histologic appearance of the pulmonary vessels in these two cases will be described together after the report of Case 4.

CASE 4.*—*Clinical History*: A 7-year-old girl was referred to the clinic on July 1, 1947, by her family physician because of tachycardia. There was no history of rheumatic fever, cyanosis, cough, or thoracic pain. Her exercise tolerance had always been normal.

Physical examination revealed that the patient was normally developed. Blood pressure readings were essentially the same in the two arms, varying from 136 to 150 systolic and from 45 to 50 diastolic. The systolic blood pressure readings in the left leg varied from 98 to 102 and the diastolic, from 50 to 60 mm. of mercury. In the apical region there was a harsh, loud systolic murmur and over the pulmonary area there was a continuous arteriovenous type of murmur. The latter murmur was also heard posteriorly. No thrill was felt on the thoracic wall, but a systolic thrill was palpable over the suprasternal notch. No cyanosis was observed in the lower extremities or in any other part of the body. The femoral arterial pulsations were forceful. Pulsations over the thoracic wall were sought, but none were encountered.

Laboratory studies revealed a trace of albumin in the urine. Examination of centrifuged specimens of urine revealed erythrocyturia, Grade 2 (on the basis of 1 to 4, in which 1 represents the least and 4 the most severe condition). There were 11.3 Gm. of hemoglobin per 100 c.c. of blood. The erythrocyte count was 3,900,000 and the leucocyte count was 6,200 per cubic millimeter of blood. A roentgenogram of the thorax showed cardiac enlargement and prominence of the hilar vessels. There were no erosions of the ribs (Fig. 10,*a*). The electrocardiogram was unusual and at the time did not contribute to the diagnosis (Fig. 10,*b*).

The clinical diagnosis was patent ductus arteriosus and coarctation of the aorta. The location of the coarctation with respect to that of the aortic mouth of the ductus arteriosus was not determined.

Operation was advised and it was performed on Oct. 16, 1947. The thoracic cavity was entered through a left posterior exposure. A severe degree of aortic coarctation which virtually closed the aortic lumen was found at a point about 1.5 cm. distal to the origin of the left subclavian artery and just proximal to the aortic entrance of a widely patent ductus arteriosus (Fig. 11,*a*). Despite the absence of prominent collateral vessels and the fear of irreversible damage from clamping the thoracic aorta for the requisite time to permit an anastomosis, reconstructive surgical treatment was undertaken. The ductus arteriosus was divided and its pulmonary end ligated. The aortic end of the ductus arteriosus was removed along with a segment of aorta containing the coarctation. Anastomosis of the ends of the aorta was accomplished.

The urinary output on the day following the operation was 1,500 cubic centimeters. On subsequent days it varied in amount between 400 and 900 c.c. a day. During the postoperative period the slight albuminuria and microscopic hematuria which had been observed preoperatively were unchanged. On Oct. 20, 1947, thirteen days postoperatively, profound shock developed and the patient died in spite of all measures of resuscitation.

Necropsy Findings.—

Gross Observations: At necropsy it was found that there had been focal separation of the suture line in the aorta which was responsible for a left hemothorax. The heart was greatly enlarged, weighing 250 grams. The normal weight of a heart of a 7-year-old girl is about 80 grams. The cardiac enlargement was caused by hypertrophy of each ventricular wall. The right ventricle measured 0.8 to 1.2 cm. in thickness; the left, from 0.6 to 1.0 cm. (Fig. 11,*b*). Neither ventricular chamber was dilated. The atria were of normal size and communicated normally with the great veins. The aortic valve was anomalous in that the left and right leaflets were interadherent by a high raphe.

*Certain data in this case report are republished with permission from Burchell, H. B.: Variations in the Clinical and Pathologic Picture of Patent Ductus Arteriosus, M. Clin. North America **32**:911, 1948.

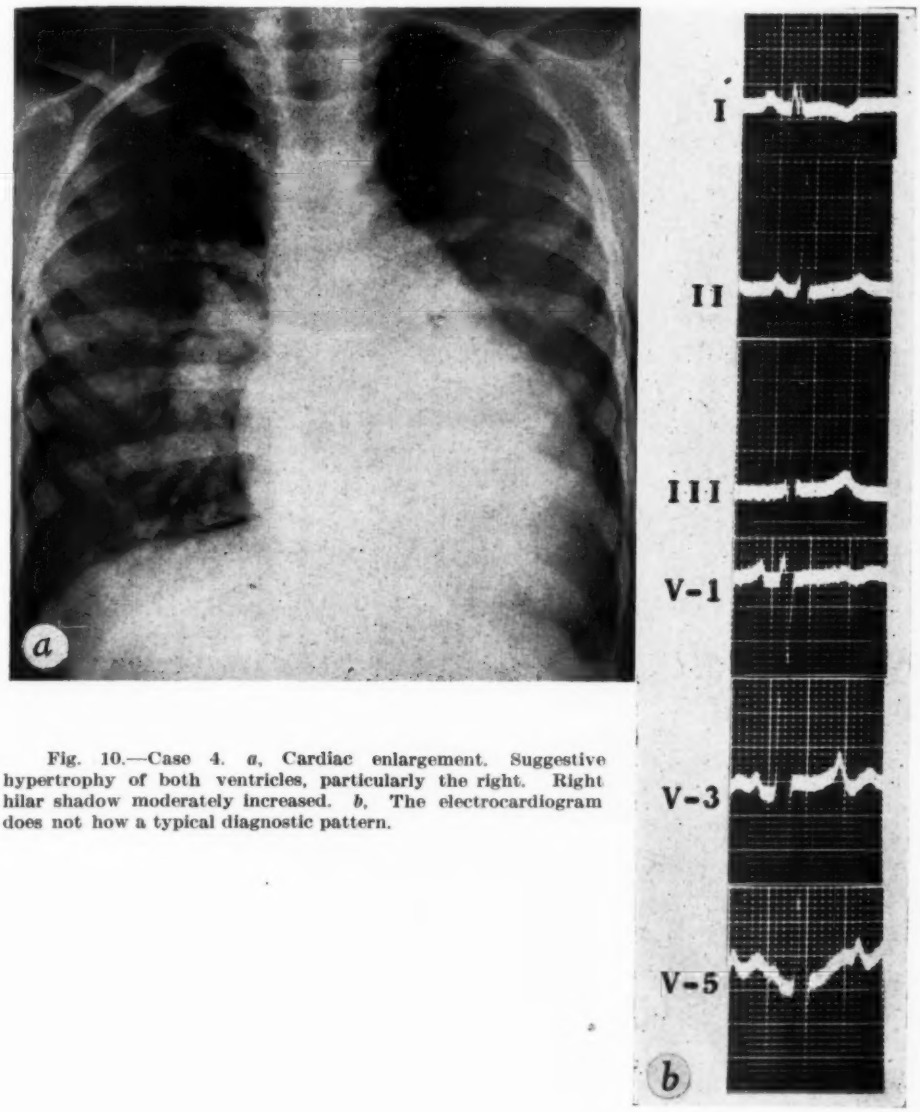


Fig. 10.—Case 4. *a*, Cardiac enlargement. Suggestive hypertrophy of both ventricles, particularly the right. Right hilar shadow moderately increased. *b*, The electrocardiogram does not how a typical diagnostic pattern.

While these two leaflets were identifiable as separate, they must have functioned as a single cusp. The posterior aortic leaflet was normal (Fig. 11,*c*). There were no other intracardiac anomalies. The pulmonary orifice measured 5.9 cm. in circumference; the aortic, 3.9 centimeters. There was little if any evidence of an enlarged collateral circulation that would bypass the aortic coarctation. The ostium of the first right aortic intercostal artery seemed somewhat wide, but the ostia of the other intercostal arteries were within normal limits of size. The necropsy revealed no evidence of enlargement of the internal mammary or of the epigastric arteries.

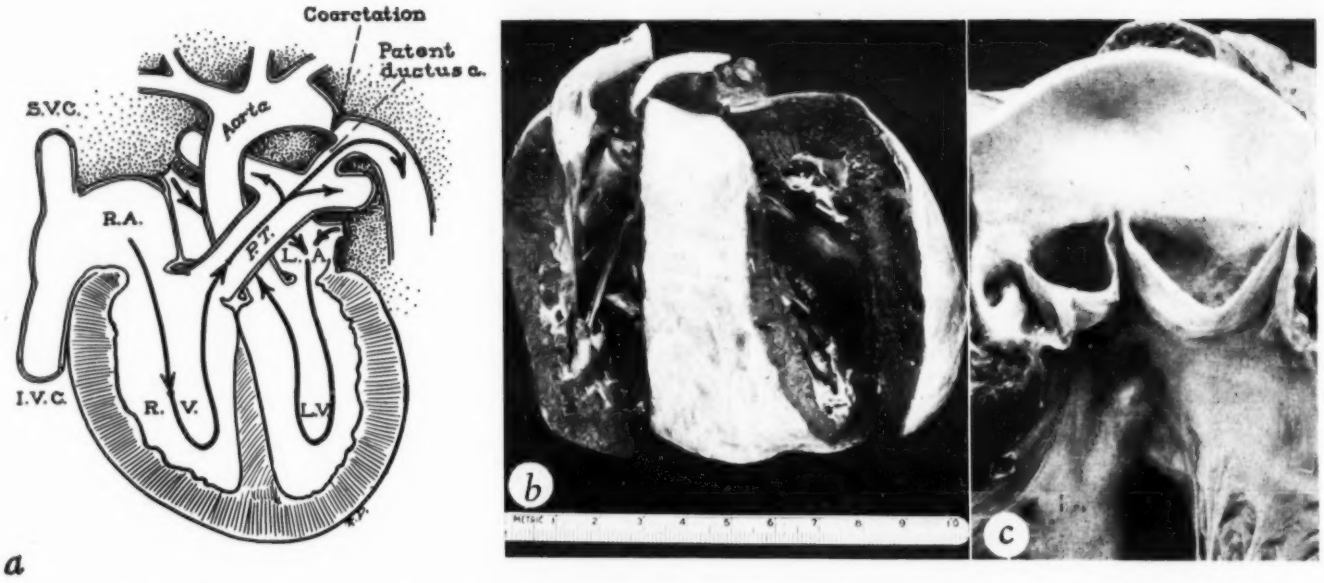


Fig. 11.—Case 4. *a*, The heart and great vessels. Composite of observations made at operation and at necropsy. There is a severe degree of aortic coarctation proximal to the entrance of a widely patent ductus arteriosus. Hypertrophy of right ventricle. *b*, The heart. Each ventricle has been opened. The right ventricle, which functioned as a systemic ventricle, is essentially of the same thickness as the hypertrophied left ventricle. *c*, The aortic valve. The right and left cusps are joined and the two function as a single leaflet rather than as two independent ones. The posterior (noncoronary cusp) is essentially normal.

There were no changes in the ribs such as those seen in the usual type of aortic coarctation. No intimal "jet" lesion was found in the left pulmonary artery. Other than atelectasis of the left lung resulting from the left hydrothorax, the lungs showed no remarkable changes grossly. The kidneys were normal grossly and microscopically.

Microscopic Observations in Cases 3 and 4.—In both Cases 3 and 4 there were morphologic changes involving most of the intrapulmonary arteries and arterioles. The microscopic findings in the lungs in these two cases, which were fundamentally alike, will be described together. Universally, the intrapulmonary arteries and arterioles showed medial hypertrophy. In many instances there were heavy bundles of collagen that constituted the adventitia of these vessels. Intimal changes, to be described, were present additionally in some of the vessels. The media of the intrapulmonary arteries of all sizes showed an abundance of muscle fibers, a phenomenon resulting in thickening of this layer. In addition, in many of such arteries measuring from 500 to 700 microns in diameter there were numerous fibers of elastic tissue intimately intermingled throughout the layer of muscle fibers (Fig. 12,*a*, *b*, and *c*). Elastic tissue changes of similar kind but of a lesser degree were observed in arteries of small caliber. The predominant changes in the smaller arteries were adventitial fibrosis and medial muscular hypertrophy. The internal and external elastic membranes stood out clearly, being much more evident than those of normal intrapulmonary arteries of like size (Fig. 13,*a*, *b*, and *c*). The changes of the intrapulmonary arteries outlined gave them the appearance of vessels of the greater or systemic circulation rather than of the lesser or pulmonary circulation. The changes described were associated with degrees of luminal narrowing (Fig. 13,*d*).

The arterioles were uncommonly prominent in appearance, a feature resulting from the thick collagenous adventitia and thick media which characterized them. These changes were consistent in all sections prepared from the lungs in both Cases 3 and 4 (Fig. 14,*a* to *d*). Some intimal changes were present in both cases, but these were particularly evident in the arterioles in Case 3 and in the small intrapulmonary arteries in Case 4. In the arteries the intimal changes, even in Case 4, were spotty. These were characterized by eccentric intimal thickening with dense collagen that contained relatively few fibroblasts (Fig. 15,*a*). No lipoid-filled cells were observed in these lesions. They had neither the appearance of atheromas nor that of organized thrombi. Arteriolar intimal changes were widespread in Case 3 (Fig. 15,*b* and *c*). These were characterized by the presence of concentric layers of fibroblasts that formed configurations which resembled the "onion peel" changes seen in peripheral arterioles in cases of malignant hypertension and in the pulmonary arterioles in certain cases of mitral stenosis.[2] The effect of the intimal fibrosis was to thicken the intima greatly and to narrow the lumen to the point of complete closure. In Case 4 a rare small artery contained an organizing thrombus. No completely organized or recanalized thrombi were found in either of the two cases. In Case 3 engorgement of the alveolar capillaries was present in small foci, but most areas were free of this change. In Case 4 a moderate amount of

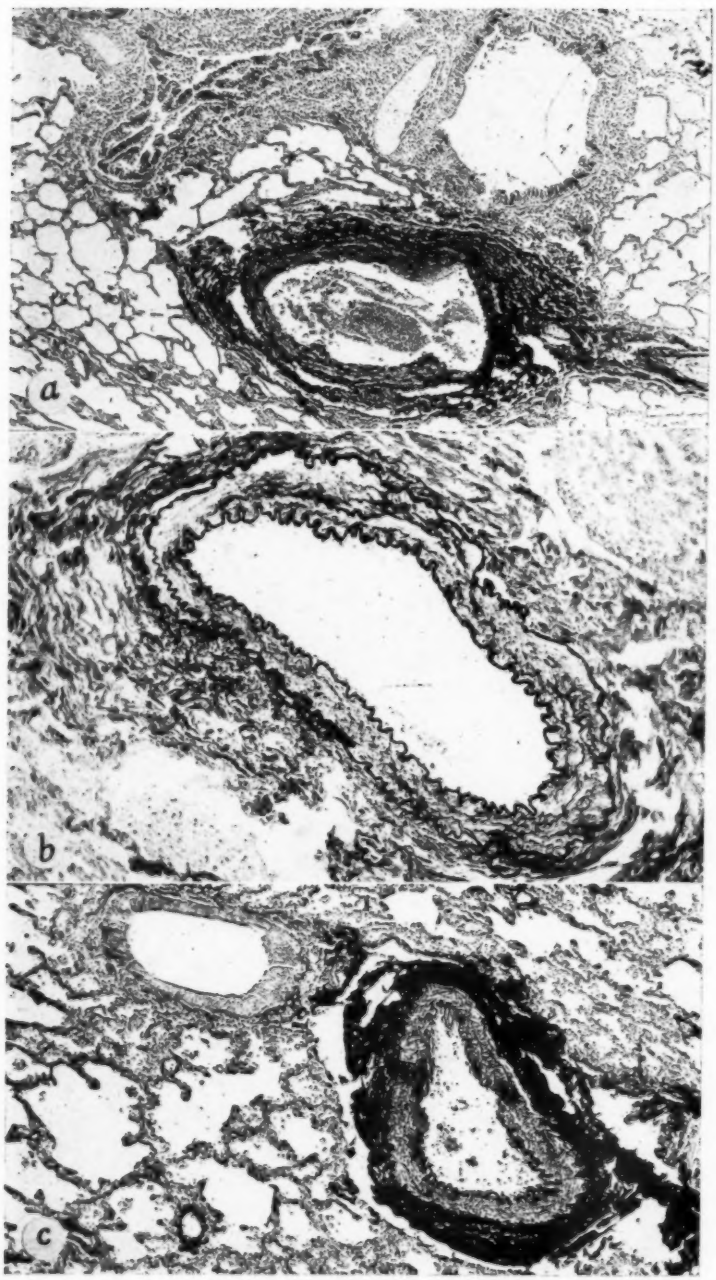


Fig. 12.—Sections of intrapulmonary arteries stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, Case 3. The media shows muscular hypertrophy and it also contains numerous elastic tissue laminae. There is some increase in adventitial connective tissue (×30). *b*, Case 4. Essentially the same medial and adventitial changes as shown in Case 3, illustrated in *a*. The medial structure is similar to that of the elastic branches of the aorta rather than to a normal pulmonary artery of like caliber (×75). *c*, Case 3. Medial hypertrophy and adventitial fibrosis (×60).

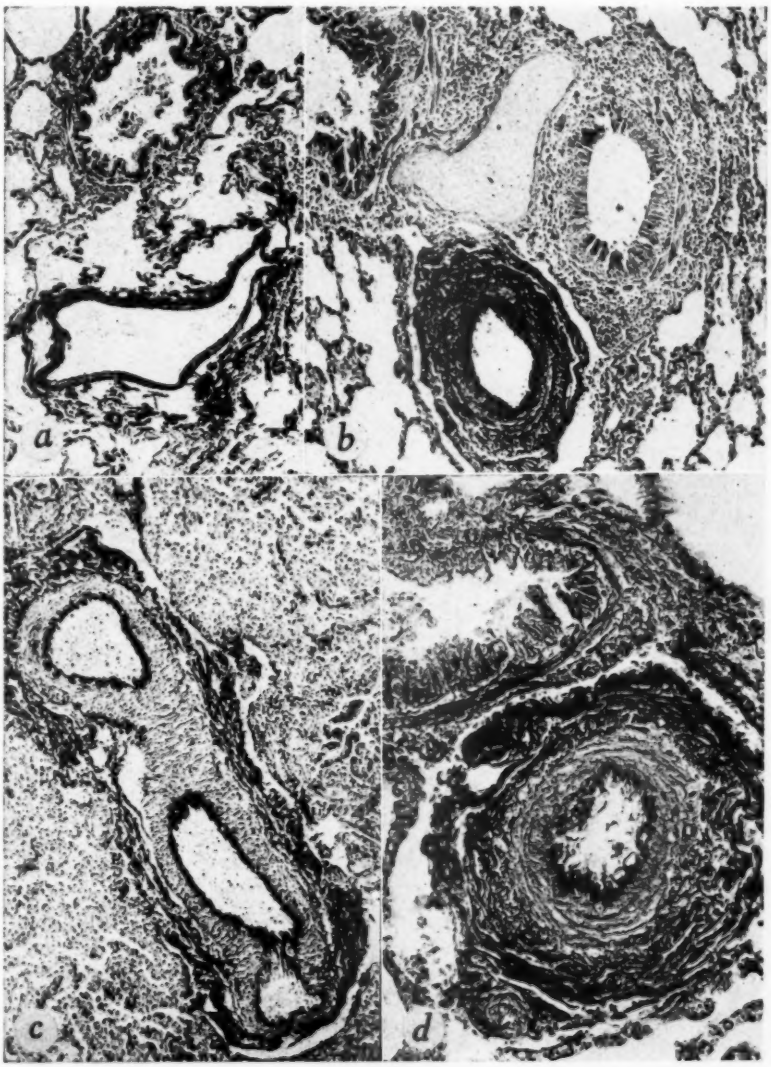


Fig. 13.—Sections of small intrapulmonary arteries stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, Normal artery from a 2-year-old boy for comparison with artery of similar size from Case 3 shown in *b* (×55). *b*, Case 3. The lumen is relatively narrow. The media is hypertrophic and the internal and external elastic laminae are prominent. There is adventitial fibrous thickening. The intima is normal in this artery. Compare with *a* (×55). *c*, Case 4. As in Case 3, the artery shows medial hypertrophy and adventitial fibrosis. The artery appears more like a peripheral artery than a pulmonary artery. The vessel is tortuous (×65). *d*, Case 3. Medial hypertrophy and adventitial fibrosis associated with luminal narrowing (×200).

congestion was evident. This may have been related to the state of shock that existed prior to death. In neither Case 3 nor Case 4 was there any fibrous thickening of the alveolar walls, or any interstitial edema. There were no histologic changes in the tributaries of the pulmonary veins.

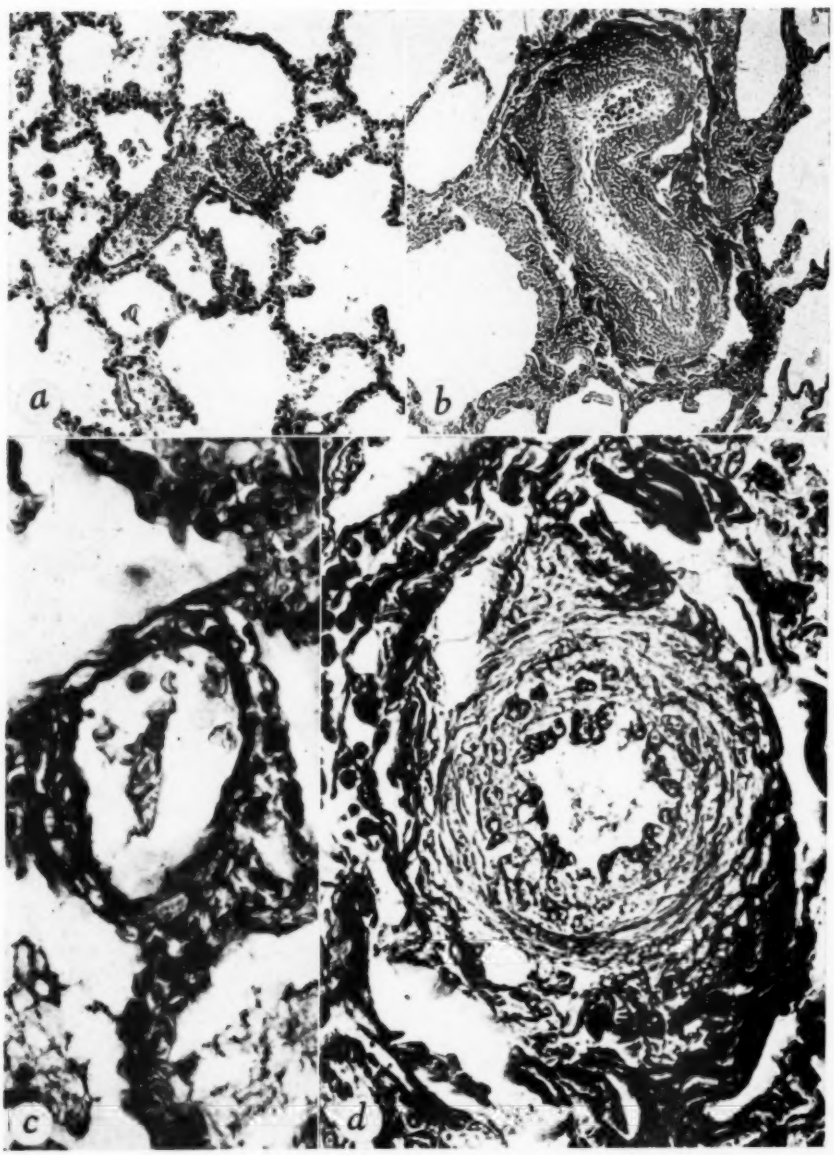


Fig. 14.—Sections of pulmonary arterioles stained with Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain. *a*, Normal pulmonary arteriole from an 18-month-old infant for comparison with one in Case 3, illustrated in *b* (×115). *b*, Case 3. Thickening of the arteriolar wall chiefly as a result of medial hypertrophy. There is also some intimal and adventitial fibrosis. Considerable luminal narrowing. Compare with normal illustrated in *a* (×115). *c*, Normal pulmonary arteriole from a 6-year-old child for comparison with one in Case 4, illustrated in *d* (×435). *d*, Case 4. Medial hypertrophy of arteriole. Adventitial fibrosis. Swollen endothelial cells. Luminal narrowing. Compare with *c* (×435).

As in Cases 1 and 2, measurements of the arteriolar luminal diameters were compared with those of normal pulmonary arterioles from individuals of ages corresponding to those of the particular subjects. The degrees of arteriolar luminal narrowing were more severe in Cases 3 and 4 than they were in Cases 1 and 2. The results are recorded in Table I. In Case 3, in which the greatest degree of arteriolar luminal narrowing occurred, the diameters of the lumina of arterioles for which the external diameters ranged from 50 to 99 microns

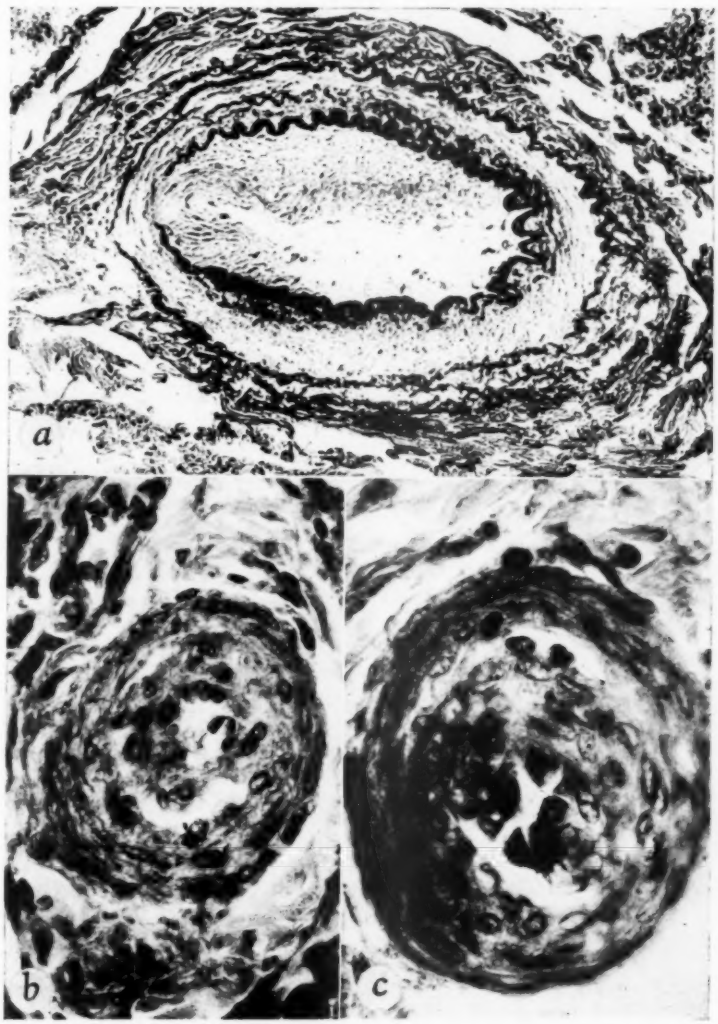


Fig. 15.—*a*, Case 4. An intrapulmonary artery showing medial hypertrophy, focal interruption of the internal elastic lamina, and focal intimal thickening with fibrous tissue (Verhoeff's elastic tissue stain and counterstained with Van Gieson's connective tissue stain, ×170). *b*, Case 3. Pulmonary arteriole showing marked luminal narrowing on the basis of laminated cellular fibrous thickening of the intima and medial hypertrophy (hematoxylin and eosin, ×460). *c*, Case 3. Pulmonary arteriole. The lumen is greatly narrowed by the cellular changes in the thickened wall. There is intimal fibrous thickening and medial hypertrophy (hematoxylin and eosin, ×620).

averaged 57 per cent of the control diameters. In that case the arterioles which measured 100 to 200 microns in external diameters showed lumina, the diameters of which averaged only 53 per cent of the control diameters. While in Case 4 the arteriolar lumina were not narrowed to the degree that existed in Case 3, they were, nevertheless, significantly narrowed. Thus, in arterioles with external diameters varying from 50 to 99 microns the arteriolar lumina were only 64 per cent as wide as the expected. In the class of larger arterioles in Case 4 the lumina were 59 per cent as wide as in control arterioles of comparable external diameters. If one averages all the arterioles measured in Cases 3 and 4, he derives the fact that the average arteriolar lumen in these two cases was only 58 per cent as wide as the average control arteriolar lumen.

COMMENT

It is of interest to discuss the aberrations of circulation in our four cases. In none had special intracardiac and intravascular studies been carried out during the respective lives of the patients. Such studies might have established certain facts from which positive deductions concerning pulmonary arterial pressures and directional flow could have been made. Nevertheless, there are sufficient morphologic alterations to justify such a discussion. Cases 1 and 2 will be considered first. It will be recalled that the basic malformation in each was the presence of aortic coarctation at a point distal to the entrance of a patent ductus arteriosus. What might have been the circulatory status of these two individuals during fetal life? Under conditions of normal fetal circulation the pressures within the two ventricles are probably equal as they are in the pulmonary trunk and its major branches on one hand and in the aorta on the other. The ready communication of the pulmonary arterial system with the aorta through the ductus arteriosus is one important factor in equalizing the pressures. Another factor is that of the intrapulmonary vessels which either by their structure or their function or both act as a sphere of relatively high resistance and so tend to divert blood through the ductus arteriosus into the descending aorta. Relatively little blood flows through the fetal pulmonary circulatory system compared with that which flows through the ductus into the aorta. We assume that the coarctation existed before birth. Thus during fetal life the right and left ventricles were in direct communication with the aorta above the coarctation. Two modes of fetal circulation may be considered. The first would have been dependent upon a greater pressure in the aortic arch than in the pulmonary arterial system. Under such circumstances the blood flowing through the ductus arteriosus would have been directed toward the left pulmonary artery, a direction the reverse of the normal for the fetus.[3] From the pulmonary arteries the blood would flow through the lungs and return to the left ventricle, whence it would again enter the aorta above the coarctation. An avenue for the free flow of blood in the course outlined would probably have resulted in an aortic pressure insufficient to stimulate the formation of adequate collaterals. In that event the aorta below the coarctation would have received little blood and the flow through the placenta would have been inade-

quate to maintain life. Since both of these individuals did have a complete fetal life, it is evident that during that period there had existed an adequate placental flow. That being the case, the conjectural course of the circulation as it has been outlined must not have been in existence.

The second alternative would have been for collateral channels to have developed to sufficient size to carry an adequate amount of blood into the lower part of the aorta. Such a collateral system existed at the time of necropsy at the ages of 15 and 22 years, respectively. That it had actually functioned while the individuals were in utero is attested to by the fact that life during that period was normally maintained. The development of a collateral system such as exists in coarctation is probably dependent upon the maintenance of a substantial blood pressure above the point of aortic narrowing. One must therefore assume that in our Cases 1 and 2 a substantial blood pressure existed in the upper part of the aorta before birth. Since the pulmonary circulation was in communication by way of the ductus arteriosus with the aorta proximal to the coarctation, there must have been sufficient resistance to pulmonary blood flow so as to support, in the proximal part of the aorta, a pressure sufficient to stimulate the formation of adequate collaterals. In a circulatory system functioning as outlined, the flow of blood in the fetal ductus arteriosus would be in a normal direction, from the left pulmonary artery into the aorta.

It is evident that the discussion of the fetal circulation in our Cases 1 and 2 pertains, as well, to all cases of coarctation of the aorta wherein the coarctation lies at a point distal to the aortic mouth of the ductus arteriosus. Under usual conditions in the individual born with this type of coarctation, the ductus arteriosus closes normally during the early postnatal period and the lungs are no longer the potential site of a shunt of blood coming from the aorta through the ductus arteriosus. In our Cases 1 and 2, on the other hand, the ductus arteriosus remained open. In the face of the normal postnatal differences between the aortic and pulmonary pressures one would expect that aortic blood would be shunted into the lungs through the ductus arteriosus. Adding the factor of hypertension as it exists in coarctation, the degree of the shunt in our Cases 1 and 2 would, all other conditions being equal, be of considerable magnitude. That such was the case for some time after birth cannot be denied, but for some time before death there were lesions in the pulmonary arterial tree which were obstructive in nature. On the basis of these lesions it is expected that the degree of resistance to pulmonary flow must have been greater than normal. Such a factor would tend to reduce the effective difference in pressures between that in the aorta on one hand and that in the pulmonary arterial tree on the other. In Case 2, in spite of the pulmonary vascular lesions mentioned, the flow through the ductus arteriosus seems to have been from the aorta into the left pulmonary artery. The evidence for this assumption lies in the fact that the associated cardiovascular lesions were essentially like those seen in cases of uncomplicated patent ductus arteriosus. These were the marked degree of left ventricular hypertrophy coupled with only a slight degree of enlargement of the right ventricle and the presence of a "jet" lesion in the left

pulmonary artery. The assumption is further supported by the high pulse pressure that had existed in the peripheral arteries during life.

The situation in Case 1 with respect to the direction of flow through the ductus appears different from that in Case 2. In Case 1 there was considerable right ventricular hypertrophy, the right ventricular wall exceeding the left with respect to thickness, and there was some dilatation of this chamber as well. The absence of a "jet" lesion in the left pulmonary artery may be used as evidence favoring the concept that if the direction of flow in the ductus arteriosus was from the aortic to the pulmonary side, the volume of such flow was not great. The presence of intermittent cyanosis of the left hand suggests that from time to time, at least, pulmonary arterial blood was entering the aorta and part of that blood found its way into the left subclavian artery, the aortic mouth of which lay opposite that of the ductus arteriosus. The low pulse pressure in the peripheral circulation is evidence favoring the hypothesis that there was probably little if any escape of aortic blood through the ductus arteriosus. The other evidence cited favors the idea that if any shunt did occur through the ductus arteriosus in Case 1 it was in the direction of pulmonary artery toward the aorta. Such a vascular phenomenon would, of course, require that the resistance to pulmonary flow be equal to or greater than the peripheral resistance. The vascular lesions in the pulmonary arterioles and the small arteries are believed related to, and indicative of, such an increased resistance. In Case 1 the load to which the right ventricle was subjected appears to have been equal to, or greater than, that of the systemic left ventricle.

The fetal circulation in Cases 3 and 4, wherein the coarctation of the aorta was proximal to the aortic entrance of the ductus arteriosus, differed profoundly from that in Cases 1 and 2, in which, as described, the coarctation was distal to the aortic mouth of the ductus arteriosus. Whereas in Cases 1 and 2 the fetal circulation varied from the normal in that an adequate collateral system had to be developed to maintain life, the fetal circulation in Cases 3 and 4 varied little, if at all, from that of the normal fetus.

In the normal fetus, that portion of the aorta known as the isthmus, which lies between the left subclavian artery and the aortic entrance of the ductus arteriosus, is quite narrow. On this basis it is felt that most of the blood which leaves the fetal left ventricle flows into the arteries arising from the aortic arch. Thus, very little left ventricular blood passes through the aortic isthmus into the descending aorta. On the other hand, a substantial portion of the blood which leaves the right ventricle flows through the ductus arteriosus into the descending aorta. Stated another way, the great proportion of blood in the descending aorta of the normal fetus is derived by way of the ductus arteriosus from the right ventricle.

During fetal life in our Cases 3 and 4, therefore, the presence of aortic coarctation proximal to the ductus arteriosus altered the circulation little, if any, from that in normal fetuses. In the normal fetus, as in Cases 3 and 4 during fetal life, the resistance to blood flow in the pulmonary circuit is either equal to or greater than the peripheral resistance. Normally at birth, as the

placental circulation is removed, the resistance to peripheral blood flow rises. At the same time the establishment of full pulmonary blood flow is associated with decreased resistance to pulmonary blood flow. These two factors seem largely responsible for a great disproportion between the peripheral and pulmonary blood pressures after birth. As a result of these pressure differences, even when the ductus arteriosus remains patent, the right ventricle no longer forces blood into the descending aorta.

On the contrary, in the ordinary case of persistent patency of the ductus arteriosus, the flow after birth is from the aorta into the pulmonary arterial system. In unusual cases of patent ductus wherein there are obstructive lesions in the pulmonary arteries and arterioles, evidence indicates that the resistance to pulmonary flow may be of such proportions that the right ventricle builds up pulmonary arterial pressures which equal or exceed the pressures in the aorta.[1,4] When this happens, the flow of blood through the ductus arteriosus from the aorta into the left pulmonary artery may be materially reduced or the flow in the ductus arteriosus may be reversed, the right ventricle forcing blood into the aorta. In such a case the right ventricular wall is hypertrophic and may exceed the left ventricle in thickness. In our Cases 3 and 4 the presence of coarctation at the aortic isthmus prevented normal dilatation of this zone of the aorta after birth. In the face of absence of obvious collateral channels, and in the presence of a patent ductus in each of these cases, it is strongly suggestive that the right ventricle continued after birth to supply blood to the descending aorta. In Case 3 part of the blood in the descending aorta would seem to have come from the right ventricle and part through the lumen of the aortic coarctation, while in Case 4 wherein the aortic lumen was practically closed and the ductus arteriosus widely patent, it would seem that virtually all of the blood in the descending aorta was derived from the right ventricle. This concept is supported by the great degree of right ventricular hypertrophy present in both Cases 3 and 4.

The blood pressure in the lower extremities in Case 3 is not known. In Case 4 systolic pressure taken in the left leg varied from 98 to 102 and the diastolic ranged from 50 to 60 millimeters of mercury. These diastolic blood pressures compare rather closely with the blood pressures taken in the arms, which received their blood from the left ventricle. It is of interest that the right ventricular thickness was similar to, and even exceeded, that of the left ventricle.

If one assumes, as we are doing, that the right ventricle was responsible for the function of a systemic ventricle in addition to supplying the lungs, one would expect that the pulmonary vessels would exert resistance to blood flow of a magnitude which would equal or exceed that of the peripheral vessels. Otherwise flow of blood to the descending aorta from the right ventricle would not be possible. Moreover, one would have to assume that the resistance to pulmonary blood flow must have exceeded that to the peripheral flow from the time of birth. That vascular changes existed in the pulmonary arteries and arterioles, which narrowed the lumina of these vessels and created resistance to pulmonary blood flow, has been brought out in the text of this communication.

Just when these changes began to develop is impossible to state from an examination of the vessels. It is known that they were well established in Case 3, in which death occurred at 23 months of age. From our concept of the functional significance of these vascular changes, we assume that they may have started to develop before birth or very shortly thereafter.

In Case 4, in which there were intact cardiac septa, the right and left sides of the heart may be considered as separate functioning units. In Case 3 there was a ventricular septal defect through which the two ventricles were in communication. In this case the two ventricles might be considered as a single functioning unit.

Anatomic variations of the pulmonary arterioles similar to those observed in our Cases 3 and 4 might be expected in other cardiovascular malformations wherein a common source supplies blood to the pulmonary and the systemic circulations. Such malformations are persistent truncus arteriosus, cor triloculare biatriatum, and the Eisenmenger complex. Studies of the pulmonary vessels in these conditions are being carried out. Preliminary studies have indicated that the vascular changes are, indeed, similar to those in our Cases 3 and 4.

SUMMARY

This is a report of four cases wherein coarctation of the aorta and patent ductus arteriosus were associated. In two cases, in which the ages were 15 and 22 years, respectively, the coarctation was distal to the aortic mouth of the patent ductus arteriosus. In the other two cases, in which the ages were 23 months and 7 years, respectively, the aortic coarctation lay proximal to the aortic mouth of the ductus arteriosus.

Changes of significant proportions involved the intrapulmonary arteries and arterioles in each case. In the first two cases the changes were most striking in the intrapulmonary arteries. These consisted of medial hypertrophy, fragmentation of the elastic laminae, adventitial fibrosis, and fibrous proliferation of the intima. The changes were associated with significant degrees of narrowing of the arterial lumina. Thrombi in various stages of organization were encountered in both cases. In one case there was hyalinization of the intimal and medial tissue. The arterioles showed scattered changes of severe degree. In general, the arteriolar walls were thickened, a change associated with relatively narrow lumina. In one of the first two cases there was evidence that the right ventricle had exerted sufficient pressure to force blood into the aorta, thus assuming the function of a systemic ventricle.

In the second group of two cases the arteries of the lungs showed medial hypertrophy and adventitial fibrosis, changes associated with luminal narrowing. The arteriolar changes in these two cases were more striking than those in the first two cases. These changes likewise consisted of medial hypertrophy and adventitial fibrosis. In one case, in addition, intimal fibrous thickening of the arterioles was diffuse. In both of these cases the evidence suggested strongly that the descending aorta was supplied with blood by the right ventricle.

REFERENCES

1. Douglas, J. M., Burchell, H. B., Edwards, J. E., Dry, T. J., and Parker, R. L.: Systemic Right Ventricle in Patent Ductus Arteriosus: Report of a Case With Obstructive Pulmonary Vascular Lesions, Proc. Staff Meet., Mayo Clin. **22**:413, 1947.

2. Parker, Frederic, Jr., and Weiss, Soma: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573, 1936.

3. Patten, B. M.: Human Embryology, Philadelphia, 1946, The Blakiston Company, pp. 682-697.

4. Chapman, C. B., and Robbins, S. L.: Patent Ductus Arteriosus With Pulmonary Vascular Sclerosis and Cyanosis, Ann. Int. Med. **21**:312, 1944.

THE WATER TOLERANCE OF THE HYPERTENSIVE PATIENT. ITS RELATION TO OPERABILITY

GEZA DE TAKATS, M.D., AND EDSON F. FOWLER, M.D.
CHICAGO, ILL.

INTRODUCTION

IN PREVIOUS communications[1] we have stressed the importance of rigid selection of hypertensive patients for sympathectomy. The grading of the patients into three well-defined groups has been of definite value (Table I). That irreversible cerebral, cardiac, renal, or peripheral vascular damage vitiates the surgical results needs no further comment. It seems, however, that the functional state of the kidney, whether involved as a primary or a secondary factor in hypertension, needs closer attention. Clinical tests, readily performed in hospital laboratories, consist of the concentration-dilution test, the fifteen-minute phenolsulfonphthalein test, and the urea clearance test. Except in a few research institutions, the inulin and inulin-Diodrast clearance has not proved to be of practical applicability, although the recently simplified technique of Landowne and Alving[2] seems to be of definite promise. It occurred to us that the customary concentration-dilution test, which measures the extreme variations of concentration and dilution under simple clinically controllable circumstances, could be made more sensitive by collecting half-hourly samples during

TABLE I. THE THREE GROUPS OF ESSENTIAL HYPERTENSION

Group 1.	Age below 40. Minimal or no detectable organic damage. Normal blood pressure on complete rest or barbiturates. Casual diastolic pressures above 100 millimeters of mercury.
Group 2.	Age from 20 to 55. Moderate vascular sclerosis in all organs. Well-demonstrable angiospasm. Diastolic pressures cannot be lowered below 110 mg. Hg by any method. Rising diastolic pressure during the course of last six months.
Group 3.	Large recurrent retinal hemorrhages and exudates or papilledema. High fixed diastolic pressure which cannot be lowered below 120 mm. of mercury. Congestive or anginal heart failure. Poor renal function. Numerous cerebrovascular accidents. An actual malignant or premalignant state of hypertension with continuous maximal angiospasm uninfluenced by either pressor or depressor stimuli.

From the Department of Surgery, University of Illinois, College of Medicine, and St. Luke's Hospital, Chicago, Ill.

Presented at the Twenty-first Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

the period of dilution and testing them for volume and specific gravity. This is the water tolerance of Adelsberg and Fox,[3] who applied it for the study of patients recovering from hepatitis.

In this communication we shall present different patterns of such tolerance curves, correlated with the hypertensive status and the postoperative course of one hundred patients. We shall then attempt to analyze the factors influencing such tolerance curves.

PROCEDURE

The patient receives nothing by mouth after 6 P.M. the night before. The bladder is emptied before the patient retires and the urine is discarded together with all other urine passed during the night. A specimen is requested at 8 A.M., after which 1,500 c.c. of water are consumed within one-half hour. No breakfast and no other liquid are permitted. Urinary samples are collected at half-hour intervals between 8 A.M. and 12 P.M. They are tested for volume and specific gravity. Obviously this is nothing but the customary concentration-dilution test except that volume and specific gravity are followed in half-hour samples. Normal subjects eliminate 1,200 to 1,500 c.c. of urine, with the peak in the first two hours; the specific gravity fluctuates inversely with the output (Fig. 1).

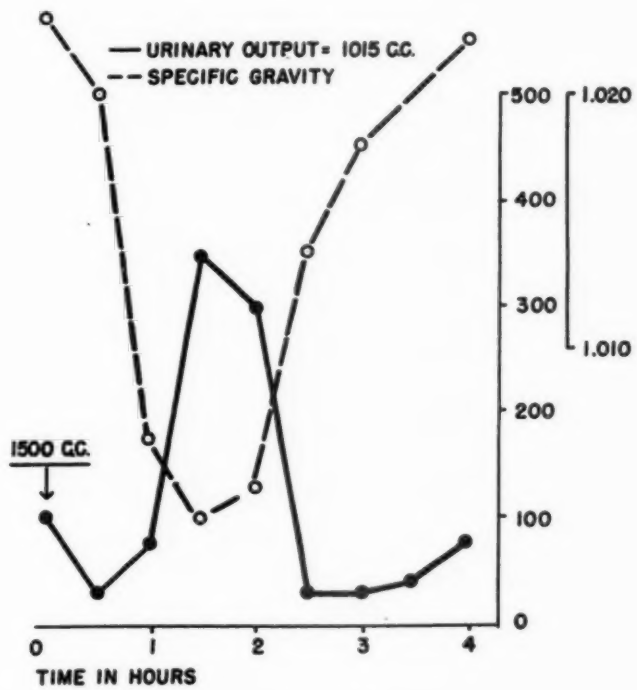


Fig. 1.—Water tolerance of Clare O., a 22-year-old man with normal cardiovascular status. Note the rapid return of specific gravity to a high level and the retention of ingested water, which seems to be a normal response of an individual restrained from drinking water for fourteen hours.

FACTORS INFLUENCING WATER TOLERANCE

We were anxious to know whether a weighed sodium and water intake prior to the test was necessary, and hence determined a few curves after sodium restriction and after excessive sodium and water intake. It did not seem that the normal individual was affected by these measures, but of course it is sufficiently known that the hypertensive individual tolerates salt restriction far better than the normal person.[4] A water tolerance test indicating unusual sodium and water retention was only considered significant for corticoadrenal activity when the patient showed a decreased response to insulin, an abnormal sugar tolerance curve, or both.[5] Such was the finding in the case of A. E., who had a left-sided corticoadrenal adenoma, proved by operation (Fig. 2). Desoxy-

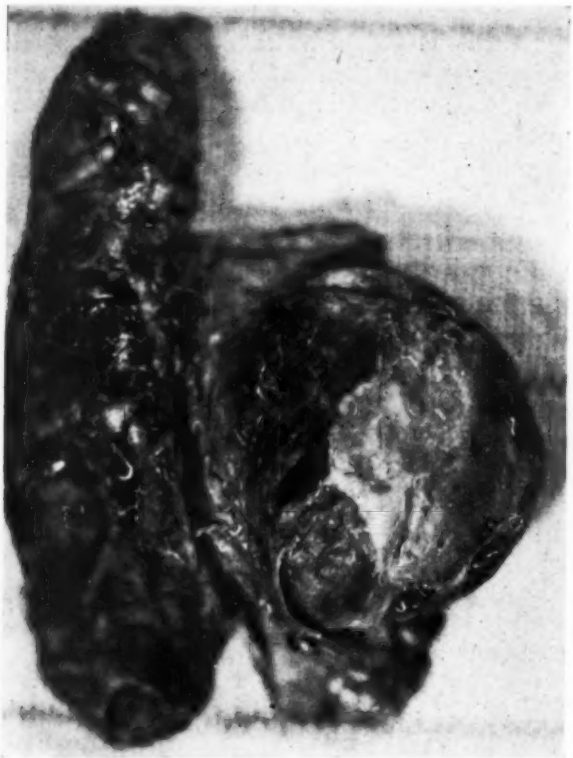


Fig. 2.—Adenoma of the left adrenal cortex removed at operation.

corticosterone acetate has a similar effect on the curve of water excretion (Fig. 3).

An inhibition of diuresis is also accomplished by *the antidiuretic hormone of the pituitary*, whose secretion is inhibited whenever water is ingested. Such a curve is shown after the injection of 1.0 c.c. of Pitressin one-half hour before

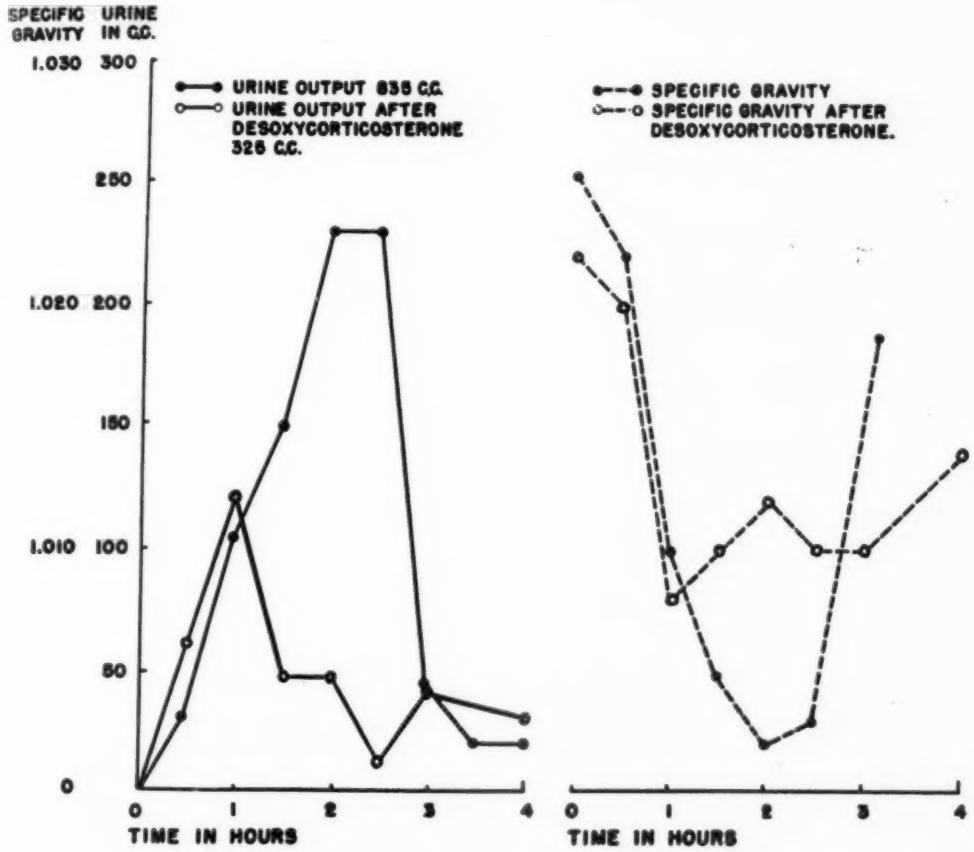


Fig. 3.—The effect of desoxycorticosterone acetate on water tolerance of Herman K.; 10 c.c. of this substance were injected intravenously the night before the tolerance was determined. Note the decrease in water excretion and the high specific gravity.

the water tolerance is started (Fig. 4). If a type of human hypertension exists which is mediated by the antidiuretic hormone, this should be demonstrable in the blood as Griffith and his associates[6] have postulated for a certain group of patients. We have no experience with this method.

Water tolerance in *hepatic disease* has been studied by Adelsberg and Fox,[3] who found significant changes in diuresis during different stages of liver disease. In the present group of patients hepatic damage could be excluded, with the exception of the middle-aged, alcoholic, atheromatous hypertensive persons, in whom we do not advocate operation. We finally come to the *renal factor*, which proved to be the most significant in this group of hypertensives who were studied for their operability. It has been our experience that of all the irreversible factors which are encountered in essential hypertension, the renal damage is most important, since, aside from the early vascular changes which may be on a functional basis and produce corticorenal ischemia,[7] the fixed

vascular and parenchymal damage in the kidney seems to be least capable of improvement compared with the regression in the eye grounds, diminution in the size of the heart, or the changes in the electrocardiogram toward normal which follows splanchnicectomy.

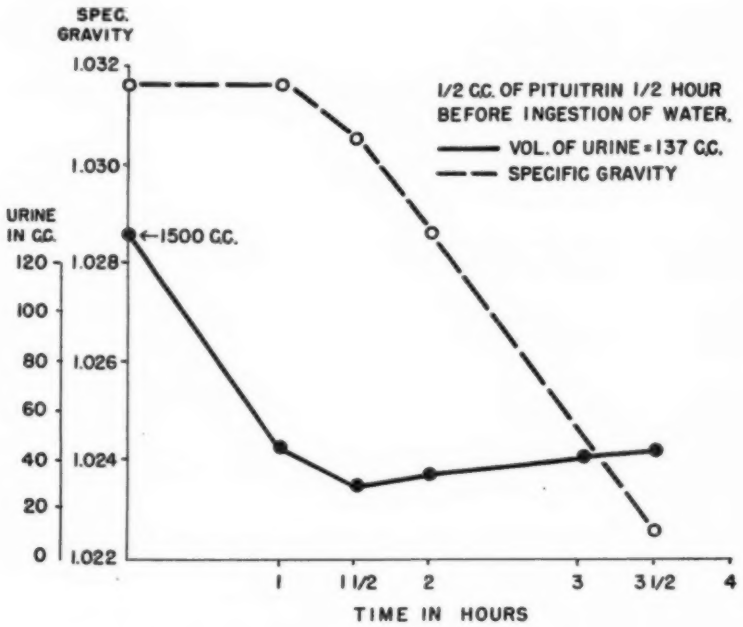


Fig. 4.—The effect of pituitrin on the water tolerance of Patrick K.

PATTERNS OF WATER TOLERANCE

From the standpoint of renal function, the concentration-dilution test has not been such a sensitive index as the water tolerance. The following six patterns have appeared after we have employed this test routinely for the past year in our preoperative studies in over one hundred patients.

Pattern 1.—(Janet J., Fig. 5.) This corresponds to the normal water tolerance as shown in Fig. 1. Fig. 5 illustrates this curve starting with a specific gravity of 1.015 which is regained in four hours. Water excretion occurs early, and after two hours not much urine is obtained. The urine showed no pathologic elements. The phenolsulfonphthalein excretion was always above 30 per cent and sometimes as high as 40 per cent in fifteen minutes. The urea clearance was above 40 c.c. per 100 c.c. of blood.

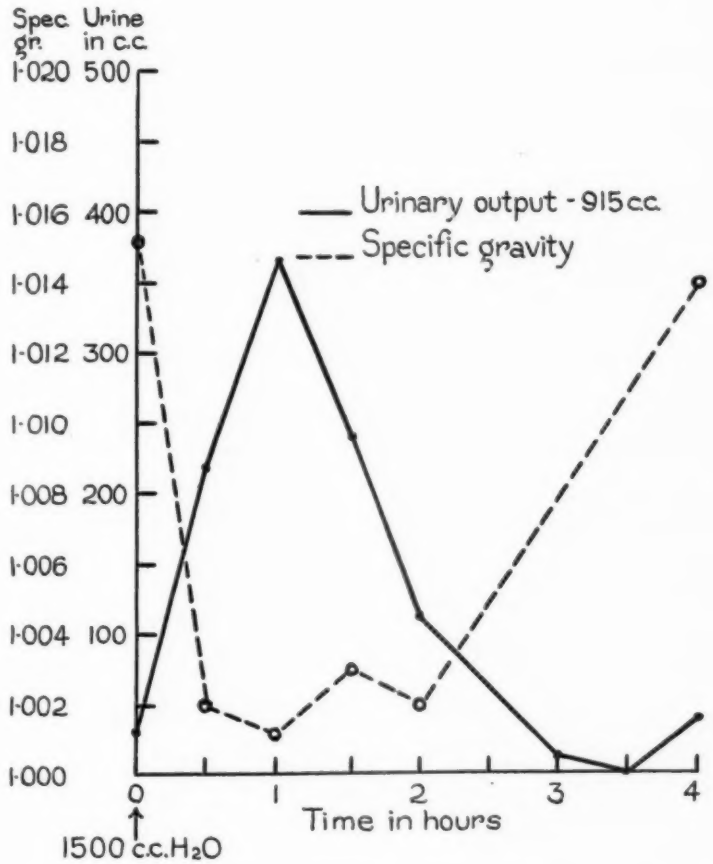


Fig. 5.—Water tolerance of Janet J., a 42-year-old married woman with Grade 2 hypertension. Duration of known hypertension, five years. Urine normal, fifteen-minute phenolsulfonphthalein excretion 30 per cent, urea clearance 42.7 cubic centimeters. Concentration-dilution, 1.015 to 1.001. Renal biopsy showed some replacement of parenchyma by fibrous tissue. Glomerular tufts showed cellular thickening and hyaline changes. Afferent arteriolar walls were slightly thickened. Lowest preoperative blood pressure 160/100. Postoperative blood pressure (thirty months follow-up) 120/80. Complete relief of symptoms.

Pattern 2.—(William L., Fig. 6.) From a specific gravity between 1.015 and 1.020 the curve drops to low figures and is only slightly regained. The ingested water is overexcreted. There is a considerable excretion of urine in the first two hours, and a plateau is not infrequent. The fifteen-minute phenolsulfonphthalein excretion in this group was just as high as in the first group, varying between 30 and 45 per cent. Their urea clearance was above 40 c.c. per 100 c.c. of blood standard clearance.

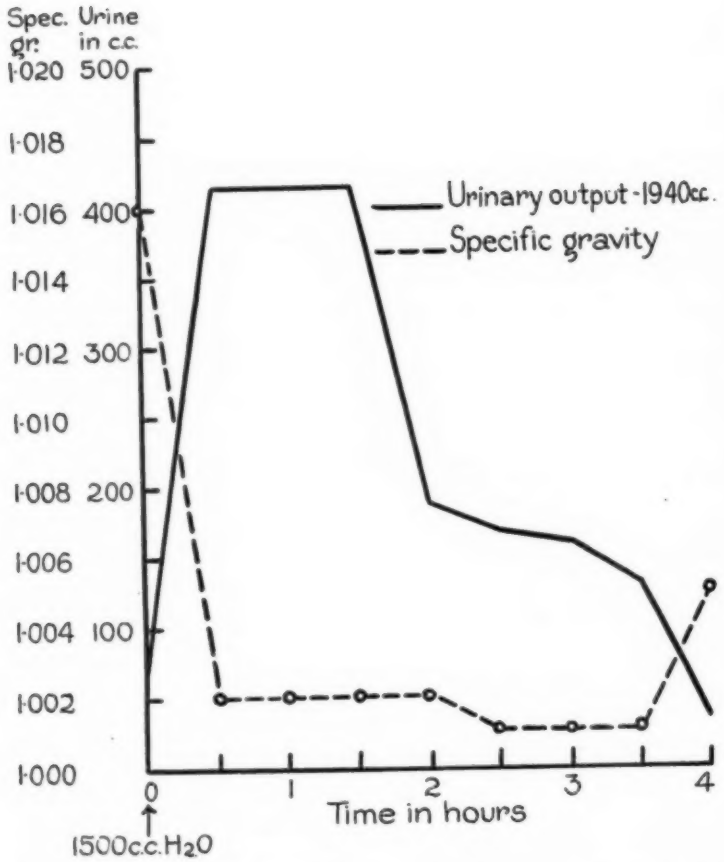


Fig. 6.—William L., a 49-year-old Grade 2 hypertensive man with a preoperative blood pressure of 220/130, a phenolsulfonphthalein excretion of 40 per cent in fifteen minutes, a urea clearance of 54 per cent, and concentration-dilution ranging from 1.016 to 1.002. However, he excreted the ingested water in four hours. Renal biopsy showed hyalinized glomeruli and increased cellular content of vascular tufts. Tubules contained granular precipitates. At discharge his blood pressure was 130/90 on lying down, with a pressure on standing of 70/0. Blood pressure after one year was 160/100.

Pattern 3.—(Edith D., Fig. 7.) This pattern starts with a high specific gravity, which drops and is hardly regained. Water excretion is definitely delayed, a shift to the right being obvious. Ingested water is overexcreted. Phenolsulfonphthalein excretion in fifteen minutes is still above 30 per cent and the urea clearance is widely fluctuating. Renal biopsies show more damage than in the previous groups.

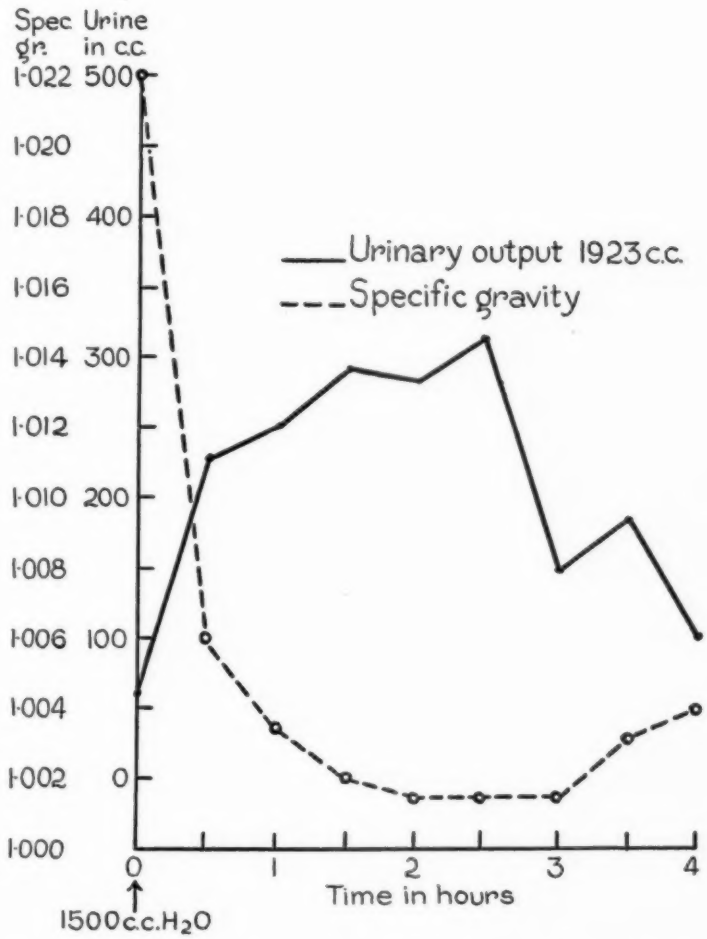


Fig. 7.—Water tolerance of Edith D., a 30-year-old housewife. Duration of known hypertension five years. Grade 2 hypertension. Urinalysis is normal. Phenolsulfonphthalein (fifteen minutes) 40 per cent, urea clearance 92.5 c.c., and concentration-dilution, 1.022 to 1.001. Renal biopsy showed capsular scarring, areas of lymphocytic infiltration, moderate hyalinization of the glomeruli, and thickened afferent arterioles. Preoperative blood pressure was 260/140. Postoperative blood pressure (three years follow-up) was 168/110.

Pattern 4.—(Florence H., Fig. 8.) This pattern starts with a fair concentration and drops to a dilution level which is maintained throughout. Water elimination occurs late, between the third and fourth hours. There is no over-excretion of water. The fifteen-minute phenolsulfonphthalein excretion is never above 20 per cent, while the urea clearance varies. Renal biopsies show Grade 3 nephrosclerosis.

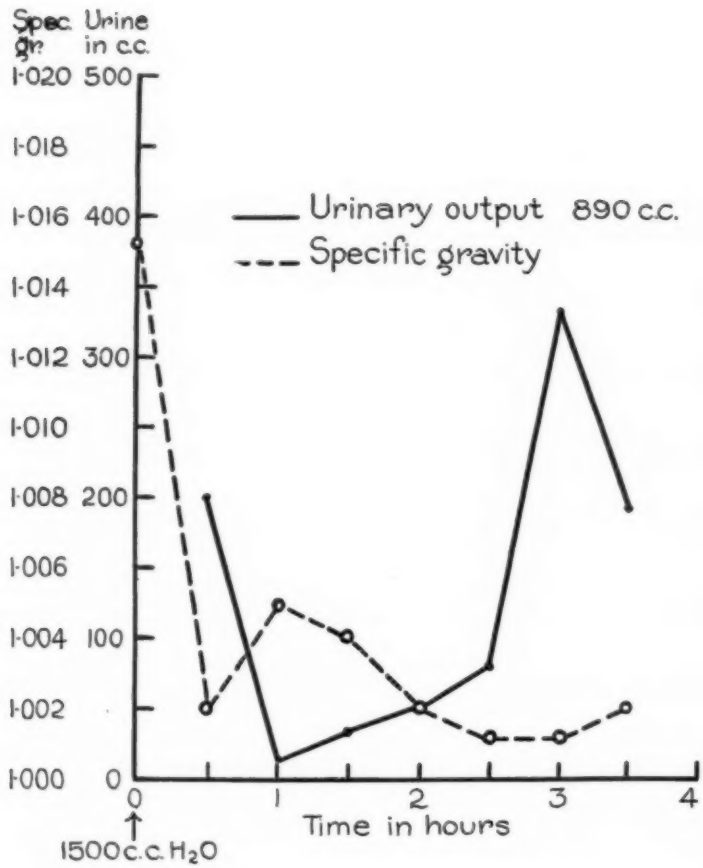


Fig. 8.—Florence H., a 52-year-old Grade 3 hypertensive woman, with a fifteen-minute phenolsulfonphthalein excretion of 10 per cent, a urea clearance of 32 c.c., and a concentration-dilution of 1.015 to 1.001. Her preoperative blood pressure was 210/120. Biopsy showed a Grade 3 nephrosclerosis. Postoperative blood pressure was 190/110 six months later.

Pattern 5.—(James R., Fig. 9.) This pattern still shows a high concentration which promptly drops to a high dilution level, but never rises again.[7] Water excretion starts after one hour, but is remarkably stable, the volume remaining fairly even throughout the four-hour period. The phenolsulfonphthalein excretion in fifteen minutes is below 20 per cent. This group shows evidence of advanced vascular sclerosis throughout the body.

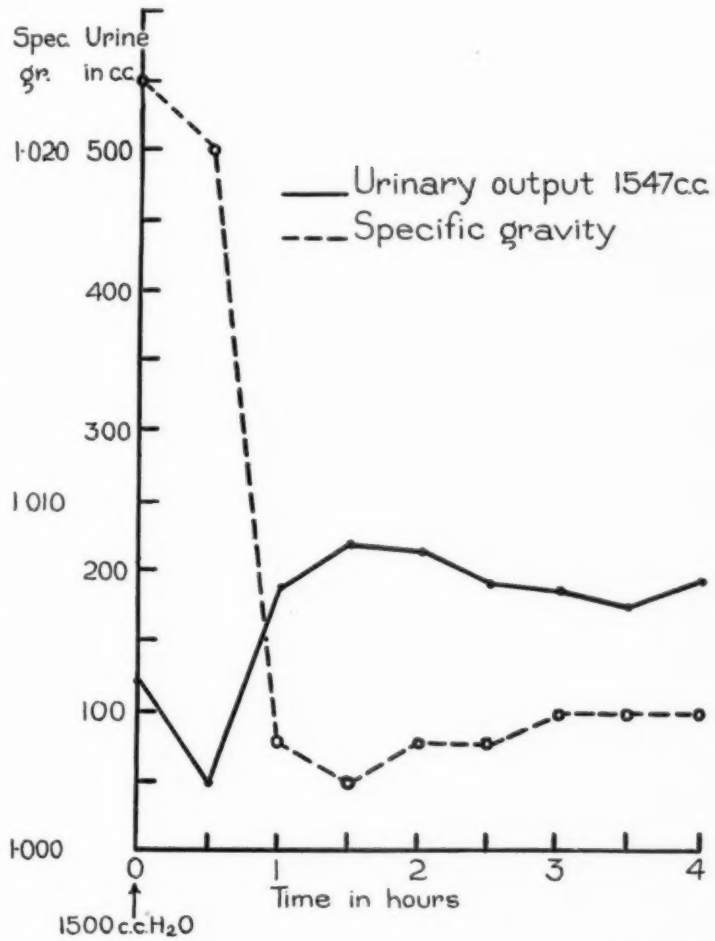


Fig. 9.—James R., a 56-year-old hypertensive man with a fixed arteriosclerotic hypertension, poor response to sodium amytal, and an excellent concentration-dilution test of 1.023 to 1.002. He was diagnosed as having an arteriosclerotic hypertension and was not regarded as a surgical case. He excreted the ingested water in four hours, but his urinary concentration remained low throughout the entire period.

Pattern 6.—(Lee L., Fig. 10.) This pattern shows high concentration, early reconcentration, and early water elimination. Both curves are highly unstable and a functional element affecting the renal vascular tree or excretory function is likely. Other renal function tests show no impairment of renal function. Such a curve may be stabilized by barbiturates or aminopyrin.

Other curves indicating a concentrating ability below 1.015 were not studied in detail since these obviously indicate advanced renal functional damage, a

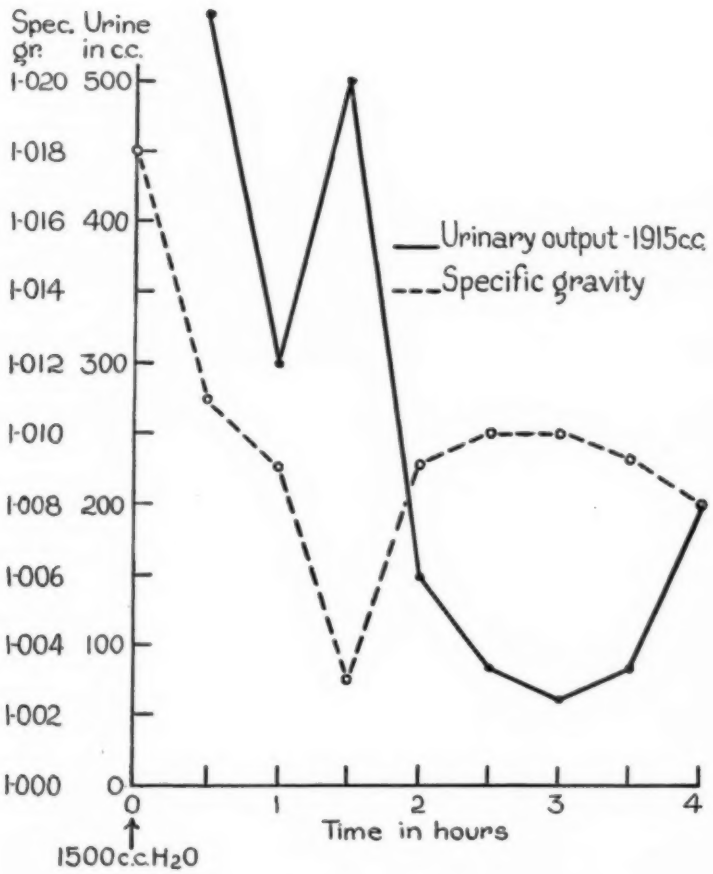


Fig. 10.—Lee L., a 49-year-old man with a Grade 2 hypertension. Duration of hypertension eight years. Urine normal, phenolsulfonphthalein excretion in 15 minutes 30 per cent. Urea clearance, 55 cubic centimeters. Concentration-dilution, 1.018 to 1.003. Renal biopsy showed moderate nephrosclerosis, Grade 1. Lowest preoperative blood pressure, 160/100; postoperative blood pressure (six months follow-up), 160/100 in the horizontal, 130/90 in the standing position. Note increased diuresis compensatory to incomplete reconcentration of urine.

hyposthenuria, or isosthenuria. However, to indicate the pattern of such a tolerance, we show the curve of Marian W. (Fig. 11), who showed a 10 per cent excretion of phenolsulfonphthalein in fifteen minutes, a fixed diastolic hypertension, and no visualization of the renal pelvis on intravenous Diodrast for a period of thirty minutes. Note the marked dilution, the overexcretion, and the complete failure to reconcentrate. This patient showed no response to splanchnicectomy, although an extended resection of the chain (D5 to L3) was done bilaterally.

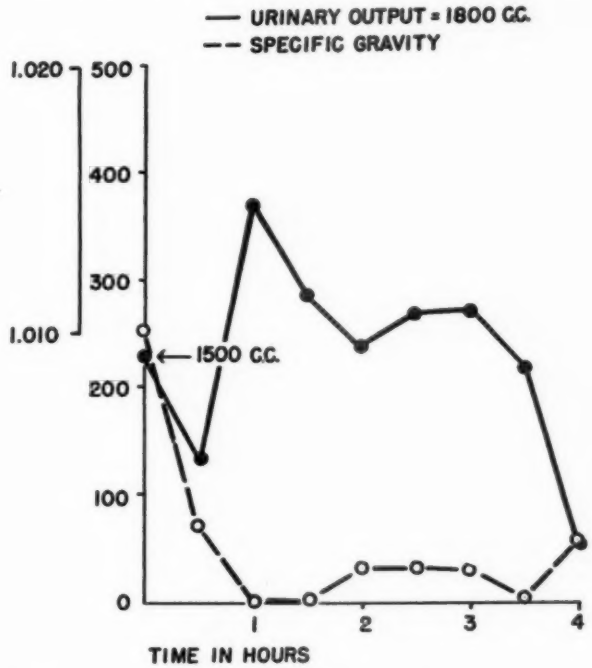


Fig. 11.—Marian W., a 34-year-old woman with a fixed diastolic hypertension between 130 and 140 mm. Hg and no visualization of the renal pelvis on intravenous Diodrast. Her fifteen-minute phenolsulfonphthalein excretion varied between 10 and 15 per cent. The urea clearance was within normal limits. Her blood chemistry was normal. The eye grounds and heart showed early (Grade 1) damage. Extensive splanchnicectomy failed to reduce her blood pressure.

THE CLINICAL SIGNIFICANCE OF THESE PATTERNS

The following table (Table II) shows the correlation of these patterns with the result obtained after sympathectomy. By failure we mean a rise of blood pressure within a year to the preoperative level. A good result is a diastolic

TABLE II. CORRELATION OF WATER TOLERANCE WITH RESULTS OBTAINED BY DORSOLUMBAR SYMPATHECTOMY

PATTERN	NUMBER OF CASES	RESULT		
		EXCELLENT	GOOD	FAILURE
1	15	13	2	—
2	42	3	39	—
3	29	—	21	8
4	9	—	1	8
5	*	*	*	*
6	5	—	5	—
Total	100	16	68	16

*No cases submitted to operation.

blood pressure stabilized between 100 and 110 mm. Hg when it was previously between 130 and 150 millimeters of mercury. An excellent result is a blood pressure below 140/90, at least one year after operation. A re-evaluation of the whole series after five years would no doubt give a smaller percentage of good results and we simply wish to illustrate a trend.

In the first two groups there were no failures and of course these belong to our intermittent or continuous but reversible stages of hypertension (Table III). The third pattern shows a great number of good results, but failures begin to occur. The fourth pattern with its failure to reconcentrate and a late water excretion has given very poor results, and the fifth pattern, since patients in this group exhibited advanced generalized arteriosclerosis, was not considered to be a surgical group. The significance of the sixth pattern is unclear and will be discussed.

TABLE III. EVOLUTION OF DIASTOLIC HYPERTENSION

	Adolescent *Intermittent* *Continuous*	
Reversible	*Partly Reversible* *Malignant*	*Irreversible*

DISCUSSION

Obviously no one test directed against a single organ can be of decisive influence regarding operability. Patients subjected to our preoperative study were examined regarding the functional status of their eye grounds, heart, peripheral circulation, and the flexibility of the vascular tree. Neither previous cerebrovascular nor coronary accidents were regarded as prohibitive indications, but advanced cerebral, cardiac, or peripheral vascular damage was regarded as prohibiting surgery. Added to this, failure to concentrate urine below 1.015 after fourteen hours of water deprivation, a fifteen-minute phenolsulfonphthalein excretion below 10 per cent of the dye, or a urea clearance of less than 20 c.c. per 100 c.c. of blood has been regarded as an argument against operation in the past.

In this series, however, we have found sixteen failures which do not fall into any of these categories. These operations were technically satisfactory and the general vascular damage was not advanced. Essentially they showed failure to reconcentrate urine in four hours, together with a late water excretion; the later the excretion, the more ominous the outlook. It should be emphasized that even Pattern 4 with one good result and eight failures shows no phenolsulfonphthalein excretion below 20 per cent in fifteen minutes and the urea clearance does not show consistent diminution below 50 per cent of normal. Ever since 1934 our group has accepted patients for splanchnicectomy with very restricted indications, and we now believe that the water tolerance test has given us one

more indication of irreversible renal damage, which neither renal nor adrenal denervation can alter. This group of sixteen patients showed a fair concentration-dilution test and would ordinarily be regarded as having sufficient renal reserve.

One cannot escape the conclusion that renal damage in hypertensive patients is more likely to be irreversible than cerebral or cardiac damage in spite of the fact that terminally renal failure is the least common cause of death. The vascular obliteration of the kidney may serve as a protective mechanism against progressive injury, but is at the same time uninfluenced by efforts of revascularization.

Patterns 5 and 6 are of special interest. Pattern 5 seems to represent the water elimination of a nephrosclerotic kidney with fixed renal function. On the other hand, Pattern 6 is certainly suggestive of emotional, neurovascular, or neurohormonal influences. Whether such a curve can be stabilized by sympathetic depressants or by central sedation is now under investigation.

SUMMARY

Normal water tolerance is defined as the ability of the individual to reconcentrate the urine during a period of four hours and to eliminate the ingested water mostly in the first two hours. Six patterns have been described which show response of the kidney to the ingestion of 1,500 c.c. of water. The patterns have been correlated with the results obtained in hypertensive patients following dorsolumbar sympathectomies. It seems that a certain group of failures could be avoided by excluding from surgery patients with crippled renal function. These patterns presumably indicate irreversible renal damage or such extra renal factors which sympathectomy does not influence.

REFERENCES

1 (a) De Takats, G., Heyer, H. E., and Keeton, R. W.: The Surgical Approach to Hypertension, J. A. M. A. **118**:501, 1942.
(b) De Takats, G., Graupner, G. W., Fowler, E. F., and Jensik, R. J.: The Surgical Approach to Hypertension. Second Report, Arch. Surg. **53**:111, 1946.
(c) De Takats, G., and Fowler, E. F.: The Surgical Treatment of Hypertension. III. The Neurogenic Versus Renal Hypertension From the Standpoint of Operability, Surgery **21**:773, 1947.
(d) De Takats, G., Julian, O. C., and Fowler, E. F.: The Surgical Treatment of Hypertension. IV. Case Selection and Technique as Influencing Results, Surgery **29**:469, 1948.

2. Landowne, M., and Alving, A. S.: A Method of Determining the Specific Renal Functions of Glomerular Filtration, Maximal Tubular Excretion (or Reabsorption) and Effective Blood Flow Using a Single Injection of a Single Substance, J. Lab. & Clin. Med. **32**:931, 1947.

3. Adelsberg, D., and Fox, L. C.: The Changes of the Water Tolerance Test in Hepatic Disease, Ann. Int. Med. **19**:642, 1943.

4. Perera, G. A., and Blood, D. W.: Disturbances in Salt and Water Metabolism in Hypertension, Am. J. M. Sc. **1**:602, 1946.

5. De Takats, G.: The Cortico-Adrenal Factor in Hypertension, Surgery. In press.

6. Griffith, J. Q., Jr., Padis, N., and Anthony, E.: Selection of Patients With Arterial Hypertension for Treatment by Repeated Injection of Pitressin, Am. J. M. Sc. **212**:31, 1946.

7. Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M., and Prichard, M. M. L.: Studies of the Renal Circulation, Springfield, Ill., 1947, Charles C Thomas, Publisher.

STUDIES ON PERIPHERAL CIRCULATION AND EPINEPHRINE SENSITIZATION FOLLOWING SYMPATHECTOMY

RALPH A. DETERLING, JR., M.D., AND HIRAM E. ESSEX, PH.D.
ROCHESTER, MINN.

WE HAVE reported elsewhere certain observations on the development of collateral circulation in dogs that had chronic femoral arteriovenous fistulas.[1,2] Lumbar sympathetic ganglionectomy performed on the side on which the fistula was located resulted in a definite augmentation of the vascular bed in the corresponding limb, as demonstrated by angiography and measurement of cutaneous temperatures of the paw.

We also performed a series of acute experiments designed to determine whether there was a correlation of the rises in peripheral cutaneous temperatures following lumbar sympathectomy with direct measurements of peripheral arterial pressure and the blood flow in certain vessels of the limb. In addition, observations were made on the effects of intravenous administration of epinephrine in the sympathectomized and the normal limb.

THE EFFECTS OF SYMPATHECTOMY ON PERIPHERAL CUTANEOUS TEMPERATURE, ARTERIAL BLOOD FLOW, AND PRESSURE

Adult dogs weighing 17 to 19 kilograms were used in this study. The animals were anesthetized by intravenous administration of pentobarbital sodium (25 mg. per kilogram of body weight). Cutaneous temperature of the paws was taken with a thermometer having a thin glass mercury bulb. The surfaces of the toes were kept dry and shaved, and the air temperature was maintained at 26° Centigrade.

The left common carotid artery was cannulated and the mean arterial pressure was found to range from 120 to 170 mm. Hg as recorded by a mercury manometer. Both femoral arteries were exposed and ligated 2 cm. below the profundus branch. Cannulas were inserted into each femoral artery proximal to the ligatures and were connected to a mercury manometer. After control pressures in each femoral artery had been obtained (Fig. 1,*a*), the vessels were divided at the site of ligation. The cannulas were then introduced into the peripheral arterial stumps to permit determination of the pressure and blood flow of the peripheral arterial or retrograde collateral circulation. Blood obtained from the femoral arterial cannulas during each direct measurement of blood flow was immediately returned to the circulation by way of a cannulated jugular vein.

From the Division of Experimental Medicine, Mayo Foundation, Rochester, Minn.

Since the lumbar sympathectomy was to be carried out transabdominally, laparotomy was performed early in the experiment to minimize the loss of blood following the administration of heparin, which was required for the experiment. At the completion of the cannulations and the laparotomy, 1,200 units of heparin were given intravenously, and 50 c.c. of a 1 to 100 solution of heparin in isotonic sodium chloride was injected by way of the jugular cannula every thirty minutes thereafter.

The following results were obtained immediately before and immediately after sympathectomy:

Results.—

A. Cutaneous Temperatures: The temperatures of both feet paralleled each other during the period before sympathectomy. Differences of 0.5 to 1.0° C. continued throughout the experiment if they were present initially. The anesthesia caused a transient rise from the control value of 31.5 to 35.0° Centigrade. The bilateral ligation of the femoral arteries just distal to the profundus branches, at the time of the cannulations, caused a rapid drop of temperature in each foot of 1.0 to 1.5° Centigrade. The temperature of the control limb then averaged 31.5 to 32.0° C. for the remainder of the experiment. After unilateral lumbar sympathetic ganglionectomy, the foot on that side became warmer at once, with a rise in temperature of 3.0° C., whereas the control side remained unchanged or became 0.5° C. cooler. This increase of cutaneous temperature on the sympathectomized side persisted throughout the period of observation.

B. Arterial Blood Flow: After the animal had been heparinized, blood flow was measured in cubic centimeters per minute directly from a T tube attached to the cannulas in the distal stumps of the femoral arteries. Five minutes after cannulation, the blood flow averaged 75 c.c. per minute from each side. In agreement with the findings of Eckstein, Gregg, and Pritchard,[3] there was a gradual increase of this flow, possibly as a result of a decrease of the peripheral resistance and an increased number of functioning vessels forming the collateral bed. After twenty to thirty minutes, the blood flow from each side was about 85 c.c. per minute, and it remained relatively constant for the subsequent observations.

Left lumbar sympathectomy was performed and immediately the retrograde blood flow from the peripheral arteries of that leg rose to 100 c.c. per minute, reaching 120 c.c. per minute in thirty minutes. This increase over control values amounted to about 40 per cent. In the control limb, the figure of 85 c.c. per minute was maintained, or reduced slightly, after contralateral sympathectomy. When a decrease of flow was observed in the control limb, there was also observed concurrently a decrease of cutaneous temperature and an increase of peripheral blood pressure.

In one experiment the continuity of the femoral arteries was re-established bilaterally by means of cannulas after sympathectomy had been performed. An increase of blood flow of 100 per cent in the sympathectomized limb over the control limb was measured from the femoral veins after cannulation. The

fact that the augmentation following sympathectomy was greater from the veins than from the retrograde arterial outflow may be explained on the basis of the difference in capacity of the arterial beds represented by each of these measurements.

The increased flow of blood following sympathectomy in all of these experiments lends support to the belief that this procedure should be expected to augment the collateral circulation of a limb after the occlusion of a major artery.

C. Peripheral (Retrograde) Arterial Pressure: Control pressures in the intact femoral arteries generally ranged between 145 and 155 mm. of mercury (Fig. 1,*a*). Subsequent mean arterial pressures were measured by mercury manometers from the cannulated peripheral stumps of the femoral arteries. Immediately after ligation of the femoral arteries, the retrograde blood pressures averaged 75 mm. Hg, or about 50 per cent of the systemic pressure (Fig. 1,*b*). There was an increase to 80 or 85 mm. Hg during the next fifteen to thirty minutes.

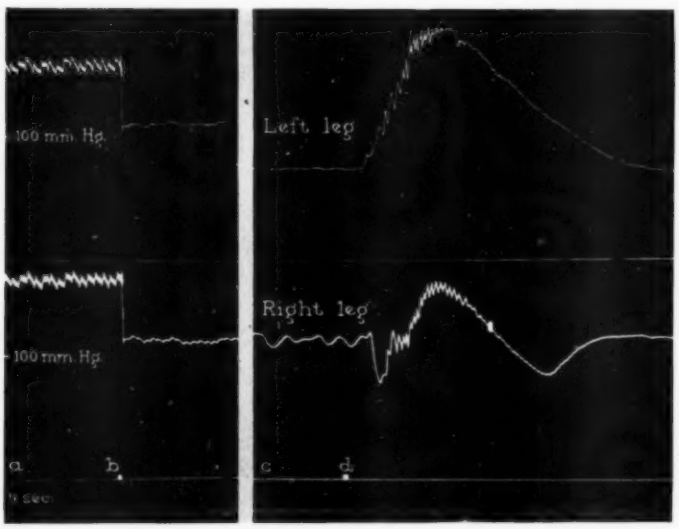


Fig. 1.—Effect of epinephrine after lumbar sympathectic ganglionectomy. *a*, Systemic arterial blood pressure obtained from both femoral arteries by direct measurement with a mercury manometer. *b*, Peripheral arterial blood pressure obtained from the distal stump of each femoral artery divided below the profundus branches. *c*, Peripheral pressures of each femoral artery immediately after left lumbar sympathetic ganglionectomy. Note the fall of pressure on the sympathectomized side, with a loss of vasomotor fluctuation. *d*, Intravenous injection of 0.05 c.c. of 1:1,000 solution of epinephrine thirty minutes after sympathectomy. Note the greater rise of blood pressure on the sympathectomized side and the longer duration of the increased blood pressure.

After sympathectomy, the retrograde arterial pressure on the ipsilateral side decreased at once to 60 to 65 mm. Hg, indicating the removal of a definite degree of peripheral resistance (Fig. 1,*c*). The unsympathectomized limb occasionally showed an increase of pressure of 5 mm. of mercury. The sympa-

thetic denervation deprived the affected vascular bed of its normal dynamic vasomotor fluctuations (compare in Fig. 1 the segment *c-d* of the left leg with that of the right).

Comment.—The results of these studies are in agreement with those of previous investigations, which demonstrated that an acute obstruction to a major arterial channel results in an immediate decrease of peripheral cutaneous temperatures, arterial flow, and arterial pressure. There soon follows a rapid, progressive rise of cutaneous temperature, blood flow, and arterial pressure distal to the occlusion, which might reasonably be interpreted as the result of improved collateral circulation, as observed after occlusion of the femoral, carotid, and coronary arteries of dogs.[3] We recognize that very rigid control must be kept over the many possible variables accompanying the measurement of cutaneous temperature if significance is to be given to the data obtained.[4] In previous studies we employed both galvanometric thermocouples and chemical thermometers, but, for convenience, in this series of experiments we employed only the thermometer. The data on cutaneous temperature that we obtained with the animals in a relatively constant environment showed a close correlation with the data obtained on arterial blood flow.

Our results varied in certain particulars from those of Theis,[5] whose methods of procedure we employed in general. Whereas we noted a consistent fall of about 25 per cent in the peripheral arterial pressure following sympathectomy (Fig. 1,*c*), Theis obtained a rise of 15 per cent, which he explained on the theory of an increase of blood flow. We accounted for our results on the theory that the decrease of the peripheral resistance resulting from sympathectomy exerted a greater influence on arterial pressure than did the increase of blood flow.

Similarly, Smithwick,[6] in reviewing 156 cases after thoracolumbar sympathectomy and splanchnicectomy for hypertension, found no drop of systemic blood pressure in only 9.7 per cent, with a decided decrease of pressure in more than 80 per cent of the cases. Leriche and Fontaine,[7] as well as Frieh and Nassi,[8] demonstrated a perisistent drop of the peripheral arterial pressure of dogs following a fleeting rise after block or extirpation of the lumbar sympathetic ganglia.

We found a 40 per cent increase of retrograde arterial blood flow following sympathectomy, as compared to 60 per cent reported by Theis. In our studies, the animals were heparinized and cannulas were used for the meaurement of blood flow. The determination of collateral arterial blood flow by direct measurement from the peripheral stump of the artery leaves much to be desired, but it was the most unequivocal method available to us at the time.

HYPERACTIVITY OF DENERVATED BLOOD VESSELS TO EPINEPHRINE

In addition to the experiments just described, studies were made of the hyperactivity of denervated blood vessels to epinephrine following sympathectomy. Increased response of smooth muscle to epinephrine following such denervation has been the source of some disagreement since the phenomenon

was first described by Meltzer and Meltzer[9] in 1903. Although most workers agree that both preganglionic and postganglionic division of the fibers will result in hypersensitivity, postganglionic division usually is considered much more effective in this respect. However, there is not complete agreement on this point. Furthermore, there has not been agreement concerning the time at which the hypersensitivity to epinephrine begins to appear. While many of the reports on sensitivity to epinephrine do not refer to a specific time of onset, those which do consider this aspect of the problem may be divided into two groups: first, those which refer to an immediate difference in the response of a sympathectomized part to epinephrine; and second, those which indicate a variable period following the denervation during which evidence of sensitization was not observed. This latter group included certain studies in which the observations were apparently not begun until several days after the denervation.

It was not our original intention to study this interesting problem, since our primary concern was with the behavior of the collateral circulation associated with a chronic arteriovenous fistula. However, during the acute experiments already described in this paper, intravenous injections of epinephrine were followed by such significant differences in the response of the sympathectomized limb as compared to the control limb that additional experiments were subsequently done.

Results.—

A. Retrograde Arterial Blood Flow and Peripheral Pressure: In three of the dogs already described in this paper, 0.05 mg. of epinephrine hydrochloride was injected intravenously thirty and sixty minutes after unilateral lumbar sympathectic ganglionectomy.

The retrograde arterial blood flow increased on both sides in response to epinephrine, but it was much greater on the sympathectomized than on the control side. It averaged 160 c.c. per minute on the sympathectomized side and 130 c.c. per minute on the control side, as compared with initial values of 120 c.c. per minute and 85 c.c. per minute, respectively.

The peripheral arterial pressure likewise rose on both sides. The blood pressure on the control side reached 180 mm. of mercury, while on the sympathectomized side it reached 230 mm., as compared to the control values of 90 mm. and 65 mm., respectively. The arterial pressure curve differed markedly on the two sides. The control side first showed a slight or moderate fall of blood pressure, which was immediately followed by a marked rise lasting one minute. The pressure then decreased from the peak to less than the control level, and recovered in twenty seconds. On the sympathectomized side, the pressure curve rose immediately from the base line to a higher peak, and decreased slowly to the base line, the entire elevation lasting three minutes (Fig. 1,*d*).

B. Blood Pressure in Uninterrupted Arteries: In three large adult dogs, after laparotomy and heparinization, the femoral arteries were exposed. Instead of interrupting the femoral arteries, we inserted special T tubes into them immediately below the profundus branches. These T tubes had an in-

side diameter of 2 mm., and were coated with silicone* to retard clotting. Mercury manometers were connected to each T tube for simultaneous recording of the lateral arterial pressures of both femoral arteries. A control tracing was also made from the left carotid artery in each instance. Fresh solutions of epinephrine hydrochloride were injected intravenously, recovery being allowed to occur between doses. The dose used throughout this experiment was 0.05 milligram.

After left lumbar sympathetic ganglionectomy it was interesting to note that a difference in the lateral pressures of the femoral arteries in response to the epinephrine was not apparent when the arterial continuity was intact. The femoral arteries were then occluded temporarily with Carrel clamps immediately proximal to the T tubes. Injections of epinephrine then caused a marked increase of height and duration of blood pressure (similar to that shown in Fig. 1,*d*,) in the sympathectomized limb over that occurring in the control limb, in all instances. When the clamps were removed and continuity of the vessels was re-established, there was again no difference of response to epinephrine in the two limbs.

Right lumbar sympathectic ganglionectomy was then performed. With the T tubes unobstructed there was again no difference in the response of either leg to the solutions of epinephrine. The pressure curves corresponded to those obtained in the control period prior to the sympathectomies. Carrel clamps were again placed proximal to the T tubes. The height and duration of both pressure curves following injection of epinephrine coincided, but were much greater than had occurred with the T tubes open.

Comment on Sections A and B.—It was interesting to note the increase of direct flow which followed the injection of epinephrine. Previous studies in this laboratory, in which flow was measured by the thermostromuhr in vessels of dogs several months after sympathectomy, had indicated that a marked decrease of flow occurred with an injection of epinephrine. The present studies were performed immediately after the sympathectomy, and utilized the distal stump of the severed femoral artery. Since retrograde arterial outflow from the stump was more easily effected by the blood in the anastomosing collateral arteries than by passage through the distal constricted arteriolar bed, this measurement cannot be compared with those on an intact vascular bed. The one salient point from both types of study is that there is a significant difference in the response of the sympathectomized side, be it a matter of minutes or months after the operation.

The significance of the recorded difference in the arterial pressure between the control and the sympathectomized limb in these experiments lies in the fact that hyperreactivity to epinephrine was demonstrated within a few minutes after the denervation. Some authors, among them Elliott,[10] Freeman and his associates,[11] and Smithwick and his associates,[12] have maintained that sensitization of denervated vessels to epinephrine is not present for about a week after sympathetic denervation.

*A product of General Electric Company (Dryfilm).

A number of variables have made a clear understanding of this problem more difficult. Meltzer noted immediate differences in response to epinephrine while he was observing the blood vessels in the rabbit's ear after removal of the superior cervical ganglion, whereas twenty-four hours were needed for the demonstration of similar differences when the iris muscle was studied in the rabbit. In similar experiments performed on the cat's eye, a lag of forty-eight hours was observed.[13,14] The nictitating membrane of the cat and the hand of the monkey and man have been employed as test organs also. Direct observation and recorded measurements of blood flow, surface temperature, arterial pressure, and strength of contraction of smooth muscle have been various means of demonstrating differences of response to epinephrine (Table I). As has been indicated earlier, our previous experiments concerned the development of collateral circulation in the dog, and consequently this animal was used for the present experiments, attention being directed primarily to the vascular system.

C. Venous Outflow: During the course of these experiments we were interested in the response to epinephrine, before and after sympathectomy, of the blood flow and pressure in the femoral veins with intact arteries. Accordingly, our initial study was made of the venous outflow. Both femoral veins were exposed and, after division distal to the profundus branches, the peripheral stumps were cannulated. In heparinized and anesthetized dogs weighing 5 to 7 kilograms the control blood flow, measured directly, averaged 12 c.c. per minute. With each injection of 0.01 c.c. of a 1 to 1,000 solution of epinephrine per kilogram of body weight, there appeared an immediate brief increase of outflow, to 15 c.c. per minute. This was swiftly followed by a diminution of outflow to a level of about 8 c.c. per minute. This outflow represents free continuous outflow from the cannula, during a period in which the blood was measured at intervals of one minute and was then slowly returned continuously by the jugular cannula. There was no musuclar activity nor alteration of posture during the measurements, since these studies were carried out on animals anesthetized by intravenous administration of pentobarbital sodium (25 to 30 mg. per kilogram).

D. Venous Pressure: Three dogs were then used for a similar study of venous pressures in the intact vein. The femoral veins were exposed and a vertical slit was made in the the wall of each vein 1.0 cm. below the profundus branches. Glass T tubes, coated with silicone, were inserted into the lumen of the vein. The upright arm of the T tube was fitted to a straight vertical glass tube of the same diameter. This tubing, which had been filled with a 1 to 100 solution of heparin, then constituted a direct pressure manometer. The dogs which had been heparinized were given graded doses of epinephrine, with time for recovery between injections. A constant response occurred in the systemic arterial pressure, as recorded from the carotid artery, for each dose of epinephrine. Doses of 0.001 mg. per kilogram and 0.0001 mg. per kilogram were the usual amounts injected intravenously. The arterial pressures recorded for these doses were 170 and 135 mm. Hg, respectively, from a control level of 115 mm. of mercury. The control venous pressures for both

TABLE I. RESPONSE OF SYMPATHECTOMIZED ANIMALS TO ADMINISTRATION OF EPINEPHRINE

DATE	AUTHOR	POSTGANGLIONIC OR PREGANGLIONIC SYMPATHECTOMY	METHOD AND ORGAN	ANIMAL	RESULTS
1903	Meltzer and Meltzer[9]	Post-	Blood vessel of ear	Rabbit	Immediate
1904	Meltzer and Auer[13]	Post-	Pupil	Rabbit	Need 24 hours
1904	Meltzer[14]	Post-	Pupil	Cat	Need 48 hours; still present 3½ months
1905	Elliott[10]		Innervation by sympathetic, all organs		Need 1 to 2 weeks
1918	Dale and Richards[15]	Post-	Leg: B.P. and plethysmograph	Cat	Epinephrine and histamine immediately, better later; present at 26 days
1932	Rosenbleuth and Cannon[16]	Post-	Nictitating membrane	Cat	Good effect noted after 4 to 5 days
1932	Danielopolu and others[17]	Post-	Leg	Man	Noted sensitivity with unilateral sympathectomy
1934	Freeman and others[11]	Post-	Digits (alcohol injection) Paw Ear Used 1:250,000 or 0.0001 to 0.0003 mg./kg./min.	Man Cat Rabbit	No temperature drop second to sixth day Noted on eighth, also eighteenth
1934	Smithwick and others[12]	Post-	Like Freeman and others maximal drop 15° F.		Nothing first week
1935	Grant[18]	Post- Pre-	Ear	Rabbit	Increased during 5 to 7 days; constant up to 15 months; post- more than pre-
1935	Hampel[19]	Post- Pre-	Nictitating membrane 1:50,000; 1:1,000,000	Cat	Rapid increase during 6 to 8 days, less in next week; maximum at 14 to 15 days
1936	White and others[20]	Post- Pre-	Hand Ear	Monkey Rabbit	Slow increase for days Maximum in second week; post- 2 to 3 times more than pre-
1937	Ascroft[21]	Post- Pre-		Monkey	Post: epinephrine sensitization increased 10 times pre-; epinephrine sensitization increased 3 times
1938	Fatherree and Allen[22]	Post-	Digits	Man	Criticism of temperature
1940	Fatherree and others[23]	5 post- 8 pre-	Digits	Man	Pre- 2 times post-; feel site more important than pre- or post-
1946	Grimson[24]	Review			Sensitivity develops rapidly but does not reach peak until within second week; persists unless regeneration occurs
1947	Deterling and Essex	Post- Pre-	Kidneys Paw	Dog Dog	Immediate effect Immediate effect

legs agreed with each other within 10 mm. of water throughout the presympathectomy period, and averaged 78 mm. of water.

It was noted that there was an immediate rise of as much as 40 mm. of water on injection of the stronger dose of epinephrine. The weaker dose was followed by a significant immediate rise of 10 to 20 mm. of water. These increases of venous pressures in all instances were synchronous with the first part of the rise of arterial pressure. During the latter part of this rise and for the remainder of the period in which the arterial pressure was elevated, the venous pressure fell to control level or several millimeters lower. In the latter instances, return to normal took place in stride with that of the arterial pressure.

Unilateral lumbar sympathetic ganglionectomy was performed in these animals, but no significant alterations of control venous pressures were noted immediately. In general, the venous pressure was slightly higher on the sympathectomized side, but the difference was only a few millimeters. Epinephrine was given as before operation. The usual pattern of an initial transient increase followed by a fall, usually to less than control level, was observed. The deviations were generally less marked on the sympathectomized than on the control side.

Comment on Sections C and D.—The alterations in the venous outflow and pressures in response to epinephrine were great enough to be considered significant. The initial rise of venous flow and pressure suggested that the more forceful contractions of the heart had preceded by a few seconds the arteriolar constriction observed peripherally, and it appeared that as a result, in this short early phase, an augmented volume of blood was moved through the limb. With the onset of the arteriolar constriction, the capillary flow was curtailed and a drop of venous flow and pressure resulted.

E. Effect of Epinephrine After Postganglionic Denervation: The evidence of immediate hypersensitivity to epinephrine following sympathectomy that we have presented so far was derived from observations on the peripheral vascular bed of the hind limbs of dogs after lumbar preganglionic denervation. We have mentioned that variation in reported results may be ascribed to differences in the species and organs studied. Most authors have also noted differences between preganglionic and postganglionic denervation. Fatherree, Adson, and Allen,[23] however, expressed the opinion that inherent differences in vasomotor activity of the digits of the hand and foot accounted for differences in the degree of response, rather than whether preganglionic or postganglionic section was performed. Since all our experiments were performed on dogs, we were interested in seeing if an immediate effect on the pattern of response to epinephrine might also be noted if postganglionic denervation were employed. For this purpose plethysmographs were made for the kidneys, and the effect of epinephrine on renal volume was observed.

Four adult dogs of large size were used for this study. Systemic blood pressure was recorded from the carotid artery by a mercury manometer. Plethysmographs made from cotton gauze impregnated with collodion were placed about the kidneys of the animal at laparotomy. Minute fluctuations

were noted on the control records and were found to correspond to fluctuations in the record of the systemic arterial pressure. With a control dose of 0.05 c.c. of a 1 to 1,000 solution of epinephrine, the carotid arterial pressure rose from 110 mm. Hg to a peak of 210 mm. of mercury. Both kidneys showed a concomitant decrease in volume of an identical degree (Fig. 2,*a*). The left kidney was then denervated of sympathetic fibers, with no alteration in systemic pressure (marked by arrow in Fig. 2). Epinephrine in the same dosage was given immediately after this denervation. Whereas the response of the right kidney was of the same magnitude as before, that of the denervated left kidney was much greater. The decrease of the volume of this organ was greater than before denervation, and was of longer duration (Fig. 2,*b*).

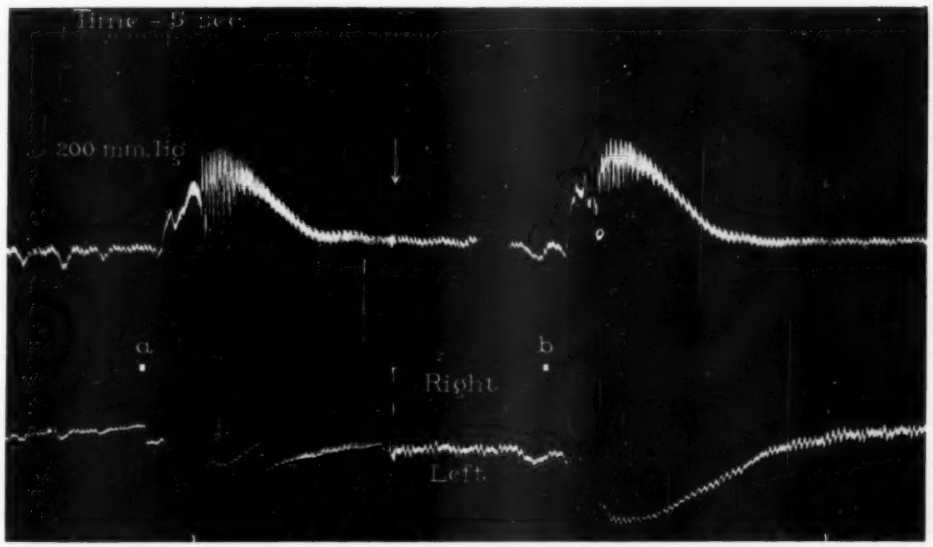


Fig. 2.—Effect of epinephrine after renal denervation. Above the base line, the systemic blood pressure is recorded by a mercury manometer from the carotid artery. Below are the plethysmographic records from the right and left kidneys. *a*, Response to 0.05 c.c. of 1:1,000 solution of epinephrine. Arrow marks the denervation of the left kidney. *b*, Response to the same dose of epinephrine after the denervation. Note the greater decrease in size of the denervated organ, and the longer duration of the effect as compared with the control side.

Comment on Section E.—Denervation of a kidney involved postganglionic denervation, in contrast to the preganglionic denervation carried out in our studies of the hind limbs. Nevertheless, we noted an excessive response to epinephrine immediately after denervation in *both* instances, even though different organs and different methods of measurement were employed.

Various hypotheses have been proposed to explain the phenomenon of epinephrine sensitization.[19,20,24] Cannon and Bacq thought that denervation permitted an accumulation of sympathin in the idle cells. When touched off by an effective stimulus, there was an excess of sympathin to react with epinephrine. Bacq later altered his ideas and claimed that the production of symthin ceased with a detoxication of the cells. This in turn resulted in a lowered

threshold to sympathomimetic polyphenols. Rosenbleuth and Cannon[16] subsequently stated that an increased permeability of the cell occurs as a result of denervation or application of cocaine. This has had support in the work of Alpern and Gabbe. Ascroft,[21] in support of Feldberg and Gaddum, found sensitivity to acetylcholine in decentralized ganglia. He expressed the belief that sensitization to epinephrine occurred as a change in or near vessels after denervation, resulting perhaps in a retardation of oxidation of epinephrine.

There have been those who maintained that degeneration of the vasomotor nerves must occur before such hypersensitivity can be detected. Smithwick, Freeman, and White[12] supported this view, and stated that sensitization was "not present after procaine hydrochloride block or during the first week after operation. We have found that it takes from seven to eight days for sensitization to appear."

These experiments clearly indicate that, as demonstrated by the methods used in this investigation, hypersensitization may occur *immediately* after preganglionic or postganglionic section of the sympathetic fibers in the dog.

SUMMARY

Experiments on dogs were performed to study the effects of lumbar sympathectomy on the peripheral circulation of the hind limbs. Significant rises of distal cutaneous temperatures and arterial blood flow and a decrease of peripheral arterial pressure followed preganglionic denervation. Epinephrine was injected intravenously immediately after unilateral sympathectomy. An increase of peripheral arterial blood pressure and flow, of greater extent and duration than on the control side, was noted. Because of the disagreement that exists as to the time of onset of sensitization to epinephrine, further experiments were performed on dogs after unilateral lumbar sympathectomy. When the continuity of the femoral arteries was maintained, no difference in the effect of epinephrine on the peripheral arterial pressures of the limbs could be demonstrated, but a difference was very evident when the peripheral arterial beds were isolated.

In control animals, administration of epinephrine resulted in a brief rise of pressure and outflow in the femoral veins, coincident with the first part of the rise of arterial pressure. The pressures and flow then abruptly decreased to the control level, or less, during the latter portion of the arterial response. This also occurred after sympathectomy, but was less marked on the denervated side.

Finally, plethysmographic studies were carried out on an intact and on a denervated kidney. Epinephrine given immediately after the postganglionic denervation similarly resulted in a greater decrease of volume and a longer duration of the effect in the denervated organ. These data suggest strongly that hypersensitivity of blood vessels to epinephrine may occur *immediately* after both preganglionic and postganglionic sympathectomy.

REFERENCES

1. Deterling, R. A., Jr., Essex, H. E., and Waugh, J. M.: Arteriovenous Fistula: Experimental Study of Influence of Sympathetic Nervous System on Development of Collateral Circulation, Surg., Gynec. & Obst. **84**:629, 1947.
2. Deterling, R. A., Jr., Essex, H. E., and Waugh, J. M.: Experimental Studies of Arteriovenous Fistula With Regard to the Development of Collateral Circulation, Proc. Staff Meet., Mayo Clin. **22**:495, 1947.
3. Eckstein, R. W., Gregg, D. E., and Pritchard, W. H.: The Magnitude and Time of Development of the Collateral Circulation in Occluded Femoral, Carotid, and Coronary Arteries, Am. J. Physiol. **132**:351, 1941.
4. Sheard, Charles: Skin Temperatures and Thermal Regulation of the Body, With Special Reference to the Extremities: Measurement and Significance Under Various Physical and Physiological Conditions. In: Glasser, Otto: Medical Physics, Chicago, 1944, The Year Book Publishers, Inc., p. 1523.
5. Theis, F. V.: Effect of Sympathetic Neurectomy on the Collateral Arteriolar Circulation of the Extremities, Surg., Gynec. & Obst. **57**:737, 1933.
6. Smithwick, R. H.: Surgical Treatment of Hypertension: The Effect of Radical (Lumbosacral) Splanchnicectomy on the Hypersensitive State of One Hundred Fifty-Six Patients Followed One to Five Years, Arch. Surg. **49**:180, 1944.
7. Leriche, René, and Fontaine, René: Mise en évidence par l'expérimentation d'un système de régulation vasomotrice périphérique indépendent de la régulation circulatoire générale, Arch. d. mal du coeur **21**:778, 1928.
8. Frieh, P., and Nassi, J.: Quelques faits expérimentaux au sujet de la scurocainisation de la chaîne lombaire comparée à ceux de la section. Effets sur la tension périphérique, Rev. de chir., Paris **74**:231, 1936.
9. Meltzer, S. J., and Meltzer, Clara: The Share of the Central Vasomotor Innervation in the Vasoconstriction Caused by the Intravenous Injection of Suprarenal Extract, Am. J. Physiol. **9**:147, 1903.
10. Elliott, T. R.: The Action of Adrenalin, J. Physiol. **32**:401, 1905.
11. Freeman, N. E., Smithwick, R. H., and White, J. C.: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenalin and to Adrenal Secretion Resulting From Insulin Hypoglycemia, Am. J. Physiol. **107**:529, 1934.
12. Smithwick, R. H., Freeman, N. E., and White, J. C.: Effect of Epinephrine on the Sympathectomized Human Extremity; An Additional Cause of Failure of Operations for Raynaud's Disease, Arch. Surg. **29**:759, 1934.
13. Meltzer, S. J., and Auer, Clara M.: Studies on the "Paradoxical" Pupil-Dilatation Caused by Adrenalin. I. The Effect of Subcutaneous Injections and Instillations of Adrenalin Upon the Pupils of Rabbits, Am. J. Physiol. **11**:28, 1904.
14. Meltzer, S. J.: Studies on the "Paradoxical" Pupil-Dilatation Caused by Adrenalin. II. On the Influence of Subcutaneous Injections of Adrenalin Upon the Eyes of Cats After Removal of the Superior Cervical Ganglion, Am. J. Physiol. **11**:37, 1904.
15. Dale, H. H., and Richards, A. N.: The Vasodilator Action of Histamine and of Some Other Substances, J. Physiol. **52**:110, 1918.
16. Rosenbleuth, A., and Cannon, W. B.: Studies on Conditions of Activity in Endocrine Organs. XXVIII. Some Effects of Sympathin on the Nictitating Membrane, Am. J. Physiol. **99**:398, 1932.
17. Daniélopolu, D., Aslan, A., and Marcou, I.: Quoted by Fatherree, Adson, and Allen.[23]
18. Grant, R. T.: Further Observations on the Vessels and Nerves of the Rabbit's Ear, With Special Reference to the Effects of Denervation, Clin. Sc. **2**:1, 1935.
19. Hampel, C. W.: The Effect of Denervation on the Sensitivity of Adrenine of the Smooth Muscle in the Nictitating Membrane, of the Cat, Am. J. Physiol. **111**:611, 1935.
20. White, J. C., Okelberry, A. M., and Whitelaw, G. P.: Vasomotor Tonus of the Denervated Artery. Control of Sympathectomized Blood Vessels by Sympathomimetic Hormones and Its Relation to the Surgical Treatment of Patients With Raynaud's Disease, Arch. Neurol. & Psychiat. **36**:1251, 1936.
21. Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities: An Experimental Analysis on Monkeys, Brit. J. Surg. **24**:787, 1937.
22. Fatherree, T. J., and Allen, E. V.: The Influence of Epinephrine on the Digital Arterioles of Man: A Study of the Vasoconstrictor Effects, J. Clin. Investigation **17**:109, 1938.
23. Fatherree, T. J., Adson, A. W., and Allen, E. V.: The Vasoconstrictor Action of Epinephrine on the Digital Arterioles Before and After Sympathectomy, Surgery **7**:75, 1940.
24. Grimson, K. S.: Sympathectomy and the Circulation—Anatomic and Physiologic Considerations and Early and Late Limitations, Surgery **19**:277, 1946.

DIFFERENTIATION OF THE CHANGES IN THE Q-T INTERVAL IN HYPOCALCEMIA AND HYPOPOTASSEMIA

A. CARLTON ERNSTENE, M.D., AND WILLIAM L. PROUDFIT, M.D.
CLEVELAND, OHIO

IT HAS been known for some time that both hypocalcemia[1,2,3] and hypopotassemia[3,4] may cause prolongation of the Q-T interval of the electrocardiogram. Little attention has been directed to the fact, however, that the electrocardiographic patterns of the two conditions can be differentiated on the basis of the length of the RS-T segments and the configuration of the T waves. In the present communication the distinguishing features of the electrocardiogram in hypopotassemia will be described and contrasted with the findings in hypocalcemia.

MATERIAL AND RESULTS

CASE 1. *Hypocalcemia Due to Idiopathic Hypoparathyroidism.*—A white, single, unemployed man, 24 years of age, was admitted to the Clinic on April 27, 1942, because of failing vision, occasional numbness, stiffness, and cramping of the hands, and inconstant difficulty in swallowing. All of the symptoms were of approximately two years' duration. The only abnormal findings on physical examination consisted of mature cataracts in both eyes, a positive Trousseau's sign, and unusual changes in the fingernails, consisting of a depression at the base of each nail. The urinalysis and blood count gave normal results, and the Wassermann reaction of the blood was negative. The serum calcium content was 4.4 mg. per 100 c.c. on the day of admission and the serum phosphorus was 5.9 milligrams. These measurements were repeated on May 2 with almost identical results.

An electrocardiogram was made on April 29 and showed changes characteristic of hypocalcemia (Fig. 1). Sinus rhythm was present with a rate of 70 per minute, and the only abnormality consisted of prolongation of the Q-T interval to 0.60 second (Table I). Correction of this value according to Bazett's formula[5] gave a constant of 0.65 (upper limit of normal for men, 0.392). The lengthening of the Q-T interval was due entirely to prolongation of the RS-T segments, which measured 0.32 second in duration, as compared with an upper limit of normal of 0.135 second in men at a heart rate of 70 per minute.[6]

CASE 2. *Hypopotassemia During and After Treatment of Diabetic Coma.*—A Negro laborer, 42 years of age, was admitted to the hospital on Oct. 9, 1946, in diabetic coma of a few hours' duration. Physical examination revealed no abnormal cardiac findings. The urine contained 4 plus sugar and 4 plus acetone, and the blood sugar content was 516 mg. per 100 cubic centimeters. The carbon dioxide combining power of the plasma was 11.8 volumes per 100 c.c. and the serum potassium content was 8.6 mg. per 100 cubic centimeters. Treatment consisted of large doses of insulin, intravenous administration of Ringer's solution, and a 500 c.c. transfusion of whole blood. The clinical response was satisfactory.

From the Cleveland Clinic.
Presented at the Twenty-first Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

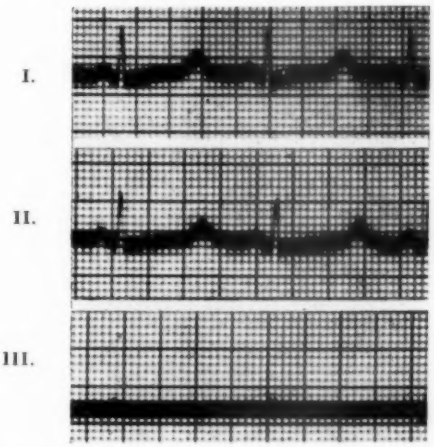


Fig. 1.—Case 1. Electrocardiogram in hypocalcemia.

An electrocardiogram taken shortly after the patient's admission showed sinus tachycardia with a rate of 102 per minute (Fig. 2). The P-R intervals and QRS complexes were of normal normal duration (Table I). The RS-T segments were of normal length but were slightly depressed in Leads II, III, and CF_4. Low, rounded T waves were present in Lead I, but the length of the Q-T interval could not be measured accurately because the descending limb of the T

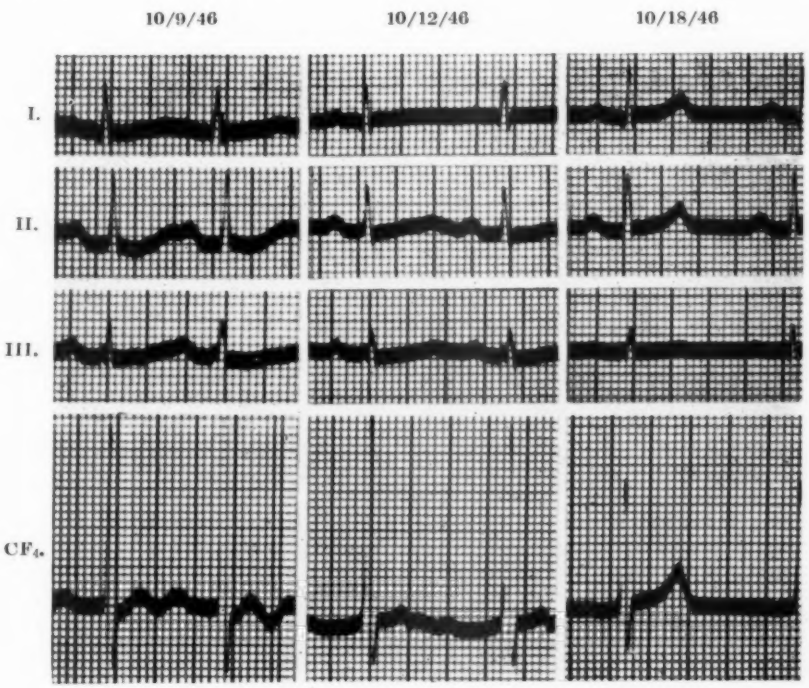


Fig. 2.—Case 2. Hypopotassemia during and after treatment of diabetic coma. The serum potassium content was 8.6 mg. per 100 c.c. on October 9, 10.5 mg. on October 12, and 21.1 mg. on October 18.

TABLE I. SUMMARY OF OBSERVATIONS

CASE NO.	SEX	DATE	ELECTROCARDIOGRAPHIC FINDINGS							SERUM CHEMISTRY	
			HEART RATE	DURATION IN SECONDS						K (MG. PER 100 C.C.)	C_a (MG. PER 100 C.C.)
				P-R	QRS	RS-T	T	Q-T	Q-T_c*		
1	M	4/27/42									4.4
		4/29/42	70	0.12	0.08	0.32	0.20	0.60	0.65		
		5/ 2/42									4.5
2	M	10/ 9/46	102	0.20	0.06	0.11	0.29	0.46	0.60	8.6	
		10/12/46	83	0.20	0.07	0.10	0.31	0.48	0.57	10.5	9.0
		10/18/46	65	0.20	0.07	0.10	0.22	0.39	0.41	21.1	
3	F	6/11/42	98	0.16	0.06	0.13	0.19	0.38	0.48	7.0	9.0
		6/18/42	103	0.15	0.06	0.11	0.14	0.31	0.40		
		6/19/42								16.0	8.7
4	M	3/ 1/43	76	0.18	0.11	0.05	0.20	0.36	0.41	7.0	9.6
		3/ 3/43	87	0.16	0.09	0.06	0.20	0.35	0.42	14.0	9.6
5	F	4/ 5/40	49	0.20	0.08	0.14	0.28	0.50	0.45	5.4	7.9
		5/ 1/40								16.1	9.8
		5/ 2/47	66	0.21	0.08	0.12	0.22	0.42	0.44		
6	F	11/ 6/46	76	0.20	0.11	0.09	0.37	0.57	0.64		11.2
		11/12/46	91	0.17	0.10	0.08	0.32	0.50	0.62	3.9	
		11/15/46								10.1	10.3
		11/16/46	83	0.16	0.08	0.06	0.20	0.34	0.40		
		11/17/46								25.4	

*Calculated according to Bazett's formula: $\text{Q-T corrected} = \frac{\text{Q-T interval in seconds}}{\sqrt{\text{Cardiac cycle in seconds}}}$

The upper limit of normal for men is 0.392 and for women 0.44.[5]

wave was deformed near its termination by a small P wave. The duration of the interval appeared to be at least 0.46 second, however, and correction of this value according to Bazett's formula gave a constant of 0.60. In Leads II and III the T waves were distorted shortly after reaching their maximum amplitude by a wave which was either a P wave or a combined U wave and P wave. Unusually prominent U waves were present in Lead CF_4 but no P waves could be identified.

On the third day after admission the serum potassium concentration was 10.5 mg. per 100 c.c., and the serum calcium was 9.0 milligrams. An electrocardiogram (Fig. 2) showed sinus rhythm with a rate of 83 per minute. The depression of the RS-T segments had disappeared. The T waves were almost flat in Lead I, but, nevertheless, were obviously much broader than normal. In Leads II and III, the T waves were low, broad, and rounded, and the duration of the Q-T interval was 0.48 second. Correction of this value according to Bazett's formula gave a constant of 0.57. No U waves could be identified in the limb leads, but in Lead CF_4 a prominent U wave was present.

On October 16 and 17 the patient was given potassium nitrate by mouth in doses of 2.0 Gm. four times daily. The serum potassium content on October 18 was 21.1 mg. per 100 cubic centimeters. An electrocardiogram made on this day (Fig. 2) showed sinus rhythm with a rate of 65 per minute. The Q-T intervals were much shorter than formerly, and correction according to Bazett's formula now gave a constant of 0.41, only slightly above normal. The T waves were sharply peaked, much narrower, and of greater amplitude in Leads I and II, but were still low in Lead III. There were no U waves in the limb leads or in Lead CF_4.

Comment: The electrocardiograms in this case illustrate the changes which result from a great reduction in the potassium content of the blood serum and demonstrate that the abnormalities are corrected by restoration of the potassium concentration to normal. The most striking changes during hypopotassemia consisted of alterations in the T waves and lengthening of the Q-T interval. In the limb leads the T waves were low, rounded, and prolonged, and it was their increased duration which was entirely responsible for the lengthening of the Q-T interval. In contrast to the electrocardiographic findings in hypocalcemia, the RS-T segments were of normal length.

When the serum potassium was at its lowest level, the RS-T segments were slightly depressed in Leads I and II, and the T waves in all three limb leads were deformed by a wave which was either a P wave or a combined U wave and P wave. An unusually prominent U wave was present in Lead CF_4. In the second record, made after the potassium concentration had risen slightly, the T waves were of smooth contour in the limb leads, and no U waves could be distinguished. A prominent U wave was still present in Lead CF_4, however, and its position suggested that a U wave might be completely fused with the T waves in the limb leads. If fusion of this kind were actually present, it could well account for at least a part of the increased duration of the T waves.

When the serum potassium content had been restored to normal, the T waves became taller, peaked, and of normal width, and the duration of the Q-T interval, corrected for the heart rate, diminished to a value only slightly above the upper limit of normal. No U waves could be distinguished in the limb leads or in Lead CF_4.

CASE 3. *Hypopotassemia Following Diabetic Acidosis.*—A white, married woman, 31 years of age, was admitted to the hospital on June 9, 1942, because of drowsiness of several hours' duration. Physical examination revealed no abnormal cardiac findings. The urine had a specific gravity of 1.029, contained a trace of albumin, and gave a 4 plus reaction for sugar and acetone. The blood sugar content was 370 mg. per 100 c.c., and the carbon dioxide combining power of the plasma was 9 volumes per 100 cubic centimeters.

During the first two days of treatment, the patient received 445 units of insulin, 1,000 c.c. of a 10 per cent glucose solution in physiologic saline solution by intravenous injection, 3,000 c.c. of a 3 per cent glucose solution by hypodermoclysis, and 500 c.c. of a 5 per cent sodium bicarbonate solution intravenously. On the morning of the third day, the fasting blood sugar content was 272 mg. per 100 c.c. and the carbon dioxide combining power of the plasma was

53.8 volumes per 100 cubic centimeters. The serum potassium content was 7.0 mg. per 100 c.c. and the serum calcium was 9.0 milligrams. An electrocardiogram made on this day (Fig. 3) showed sinus rhythm with a rate of 98 per minute. The P-R intervals, QRS complexes, and RS-T segments were of normal duration (Table I). The Q-T interval measured 0.38 second, and correction according to Bazett's formula gave a constant of 0.48. The upper limit of normal for this value in women is 0.44.[5] The T waves were broad, low, and moderately rounded in Leads I and II and were diphasic and low in Lead III. A small U wave could be distinguished inconstantly in Lead II.

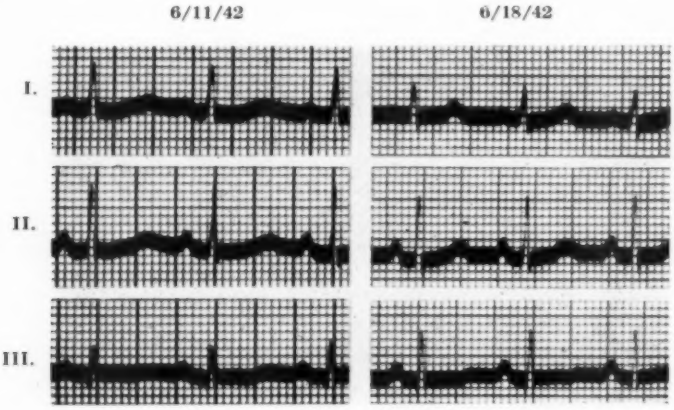


Fig. 3.—Case 3. Hypopotassemia following diabetic acidosis. The serum potassium content was 7.0 mg. per 100 c.c. on June 11 and 16.0 mg. on June 19.

The subsequent clinical course was uneventful, and the blood sugar content was satisfactorily regulated by diet and insulin. An electrocardiogram made one week after the first record (Fig. 3) showed sinus tachycardia with a rate of 103 per minute. The T waves, although of approximately the same amplitude as formerly, were sharper and narrower. The duration of the Q-T interval was 0.31 second, and correction according to Bazett's formula gave a constant of 0.40, a normal value. On the morning after this record was made the serum potassium content was 16.0 mg. per 100 c.c. and the serum calcium was 8.7 milligrams.

Comment: Hypopotassemia in this patient, as in Case 2, caused prolongation of the Q-T interval due entirely to increased duration of the T waves. The length of the RS-T segments was not affected. The T waves were low and rounded in Leads I and II of the tracing made while the serum potassium content was low. Although the return of the potassium content to normal did not appreciably affect the amplitude of these waves, the waves did become narrower and peaked, and there was a simultaneous return of the Q-T interval to normal length. Unlike the findings in the preceding case, hypopotassemia in this instance did not cause the appearance of prominent U waves.

CASE 4. *Hypopotassemia Following Diabetic Acidosis.*—A white male student, 20 years of age, was admitted to the hospital on Feb. 26, 1943, in a semistuporous condition. Physical examination revealed no abnormal cardiac findings. The urine had a specific gravity of 1.025 and contained 1 plus albumin, 4 plus sugar, and 4 plus acetone. The blood sugar content was 560 mg. per 100 c.c. and the carbon dioxide combining power of the plasma was 11.8 volumes per 100 cubic centimeters.

Treatment consisted of large doses of insulin and the intravenous administration of 1,000 c.c. of a 10 per cent glucose solution in physiologic saline and 500 c.c. of a 5 per cent sodium bicarbonate solution. On the morning after admission the fasting blood sugar content was 116 mg. per 100 c.c., the carbon dioxide combining power of the plasma was 39.5 volumes per 100

c.c., the serum potassium concentration was 6.6 mg. per 100 c.c., and the serum calcium was 10.1 milligrams. The blood sugar content subsequently remained well controlled.

An electrocardiogram was made on March 1 and showed sinus rhythm with a rate of 76 per minute (Fig. 4). The P-R intervals were of normal length, but the QRS complexes were prolonged to 0.11 second (Table I). The Q-T intervals were slightly longer than normal and the T waves were low and rounded in all leads. U waves were present in Leads II and III (although they could be distinguished only with difficulty) and by partial fusion with the descending limb of the T waves gave the superficial appearance of considerably prolonged Q-T intervals. The serum potassium content on the morning the record was made was 7.0 mg. per 100 c.c. and the serum calcium was 9.6 milligrams.

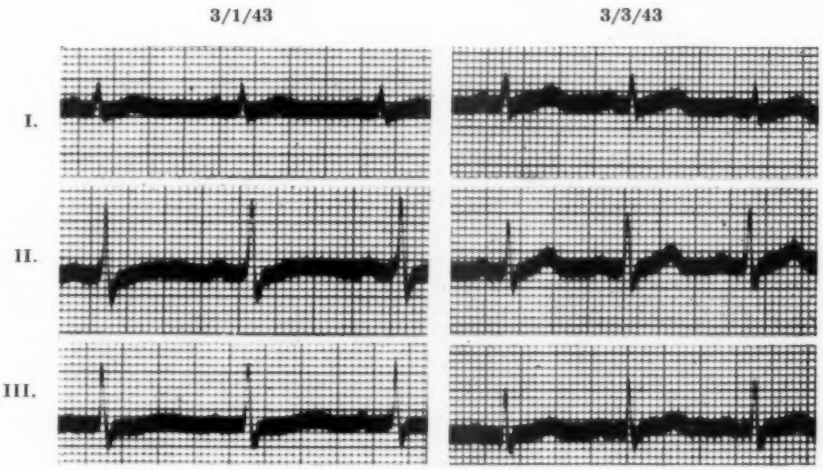


Fig. 4.—Case 4. **Hypopotassemia following diabetic acidosis. The serum potassium content was 7.0 mg. per 100 c. c. on March 1 and 14.0 mg. on March 3.**

The patient received 8.0 Gm. of potassium nitrate in divided doses by mouth on March 2. On March 3 the serum potassium content was 14.0 mg. per 100 c.c. and the serum calcium 9.6 milligrams. An electrocardiogram showed sinus rhythm with a rate of 87 per minute. The P-R intervals and QRS complexes were of normal duration. The length of the Q-T intervals was essentially the same as in the earlier record, but the T waves were of greater amplitude and peaked in all leads, and the U waves had disappeared.

Comment: In this case the duration of the Q-T interval and the width of the T waves were not affected by a rise in the serum potassium content from 7.0 mg. to 14.0 mg. per 100 cubic centimeters. When the serum potassium concentration was at the lower level, however, the T waves were low and rounded, and the duration of the QRS complexes was slightly increased. U waves were present in Leads II and III and by partial fusion with the descending limb of the T waves resulted in what at first glance appeared to be a prolonged Q-T interval. When the serum potassium content rose to 14.0 mg. per 100 c.c., the T waves increased in amplitude and became sharper, the duration of the QRS complexes returned to normal, and the U waves disappeared. The duration of the Q-T interval was still slightly greater than normal, and it is possible that a further rise in the serum potassium concentration might have resulted in narrowing of the T waves and a consequent return of the length of Q-T to normal.

CASE 5. *Hypopotassemia Due to Overtreatment With Desoxycorticosterone Acetate.*—A white widow, 40 years of age, who had been under treatment for Addison's disease for three years, received subcutaneous implants of desoxycorticosterone acetate on Oct. 3, 1939, and Jan. 5, 1940, in amounts of 198.0 mg. and 256.0 mg., respectively. Additional measures of treatment

after the first implant consisted of a diet low in potassium content with 20.0 Gm. of sodium chloride added daily, aqueous adrenal cortical extract in amounts ranging from 1.0 to 10 c.c. daily, and desoxycorticosterone acetate in doses varying from 5.0 mg. every other day to 10.0 mg. daily. On March 5, 1940, because of persistent and increasing weakness, drowsiness, headache, occasional periods of confusion, and intermittent pain in the abdomen, the pellets of desoxycorticosterone acetate were removed. The potassium content of the blood serum on the preceding day had been 5.7 mg. per 100 cubic centimeters. The diet and supplementary sodium chloride were continued as before, and the patient also continued to receive desoxycorticosterone acetate in doses of 5.0 or 10.0 mg. daily. There was considerable improvement, but occasional periods of weakness, muscular pain, abdominal distress, and edema about the eyes continued to occur.

An electrocardiogram on April 5, 1940 (Fig. 5), showed sinus bradycardia with a rate of 49 per minute. The P-R intervals and QRS complexes were of normal duration (Table I). The RS-T segments were of normal length, but were slightly depressed in Leads I and II and slightly elevated in Lead III. The striking feature of the record consisted of low, rounded T waves of increased duration in all limb leads. The Q-T interval measured 0.50 second and correction according to Bazett's formula gave a constant of 0.45. In Leads II and III the T waves merged with a U wave before returning to the isoelectric level, and this gave the appearance of considerable lengthening of the Q-T interval in these leads.

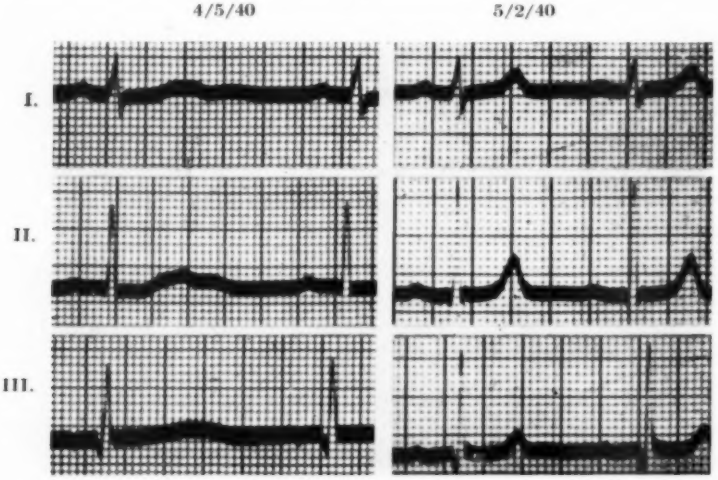


Fig. 5.—Case 5. Hypopotassemia due to overtreatment with desoxycorticosterone acetate. The serum potassium content was 5.4 mg. per 100 c. c. on April 5 and 16.1 mg. on May 1.

Physical examination on the day of this record revealed a poorly nourished, rather apathetic individual. The temperature was 98° F., and the blood pressure was 108/70. There was slight edema about the eyes. The heart and lungs were normal on percussion and auscultation. There was no peripheral edema. Urinalysis gave normal findings except for a faint trace of albumin and 10 to 12 pus cells per high power field in the sediment. The red blood cell count was 3,940,000 and the hemoglobin content 71 per cent. The white blood cell count was 5,850. The serum potassium content was 5.4 mg. per 100 c.c. and the serum calcium 7.9 milligrams.

The administration of desoxycorticosterone acetate was discontinued on April 9. On May 1 the serum potassium content was 16.1 mg. per 100 c.c. and the serum calcium 9.8 milligrams. An electrocardiogram (Fig. 5) on the following day showed sinus rhythm with a rate of 66 per minute. The P-R interval measured 0.21 second but the QRS complexes, RS-T segments, and

Q-T intervals were of normal duration. The record was strikingly different from the earlier tracing, however, in that the T waves were of greater amplitude, decidedly narrower, and peaked in all leads. The prominent U waves formerly present were not longer discernible.

Comment: In this case the Q-T interval was not significantly prolonged during hypopotassemia, and the duration of the corrected interval remained essentially unchanged after the potassium content of the serum had returned to normal. During hypopotassemia, however, the T waves were low, rounded, and of increased duration in all leads, and in Leads II and III they merged with a U wave before returning to the isoelectric level. This fusion of T waves and U waves gave the appearance of considerable lengthening of the Q-T interval in the latter leads. After the serum potassium content had returned to normal, the T waves were of greater amplitude, peaked, and decidedly narrower in all leads and the formerly prominent U waves were no longer present.

The findings in this case, when considered in conjunction with those in the preceding cases, indicate that the earliest electrocardiographic change in hypopotassemia consists of rounding, widening, and usually diminution in amplitude of the T waves. Whether or not the Q-T interval becomes prolonged is determined solely by the degree to which the duration of the T waves is increased.

The first electrocardiogram in this case was made at a time when the serum calcium content was 7.9 mg. per 100 c.c., but the absence of significant lengthening of the RS-T segment and Q-T interval indicates that the hypocalcemia had no effect upon the record.

CASE 6. *Hypopotassemia of Uncertain Cause.*—A white, single girl, 18 years of age, was admitted to the hospital on Nov. 5, 1946, because of persistent but variable edema of the face, hands, abdominal wall, and lower extremities, two years in duration. The illness apparently had begun shortly after she had broken her engagement to be married, and a brother had been severely burned in an accident. An accurate dietary history could not be obtained, but the appetite had been poor and the food intake definitely restricted. Occasionally there was vomiting after a meal. In an effort to control the edema, laxatives had been taken each night since the onset of the illness, and these had produced a chronic, watery diarrhea. The menses had been normal until a period of amenorrhea which lasted from July, 1945, until May, 1946, and following this they were irregular in regard to interval and duration. For three months before her admission the patient had received daily injections of a mercurial diuretic. There had been rapid fluctuations in the body weight, and at different times she had weighed as little as 90 pounds and as much as 134 pounds.

Physical examination revealed a small, poorly nourished girl with scanty axillary and pubic hair, dry skin, and brittle nails. The temperature was 97.8° F., the pulse rate 92, and the blood pressure 90/40. The pupils reacted normally, and ophthalmoscopic examination showed no diagnostic changes. The lungs were clear and the heart normal except for a moderate systolic murmur at the apex. The deep reflexes were sluggish in the arms and could not be obtained in the lower extremities. There was slight pitting edema of the legs.

The urine contained a trace of albumin, an occasional hyaline or finely granular cast, and a rare red blood cell. The blood count was normal. The blood urea content was 100 mg. per 100 c.c., the serum calcium 11.2 mg., and the serum phosphorus 4.3 milligrams. The total serum protein content was 6.2 grams per 100 c.c. and the Wassermann reaction of the blood was negative.

An electrocardiogram was made on the day after admission and showed sinus rhythm with a rate of 76 per minute (Fig. 6). The P-R intervals were of normal length, but the QRS complexes were prolonged to 0.11 second (Table I). The RS-T segments were of normal duration but were slightly depressed in all leads. The Q-T interval was prolonged to 0.57 second and correction according to Bazett's formula gave a constant of 0.64. The T waves were low in Lead I and large, rounded, and broad in Leads II and III. No U waves were apparent in the limb leads, but in Lead CF_4 the T waves had two peaks and the second of these appeared to be a U wave. It seemed probable, therefore, that the increased broadness of the T waves in the limb leads was due in part to fusion with a U wave.

Because of the electrocardiographic findings the serum potassium was measured on November 12, and another electrocardiogram was made. The serum potassium content was 3.9 mg. per 100 cubic centimeters. The electrocardiogram (Fig. 6) showed sinus rhythm with a rate of 91 per minute. The P-R interval and QRS complexes were of normal duration. The RS-T segments were of normal length but were depressed in Leads I, II, and CF_4. The Q-T interval was prolonged to 0.50 second and correction according to Bazett's formula gave a constant of 0.62. The T waves were broad in all leads, low in Lead I, and prominent and rounded in Leads II and III. No U waves could be distinguished in the limb leads, but a probable U wave was present in Lead CF_4.

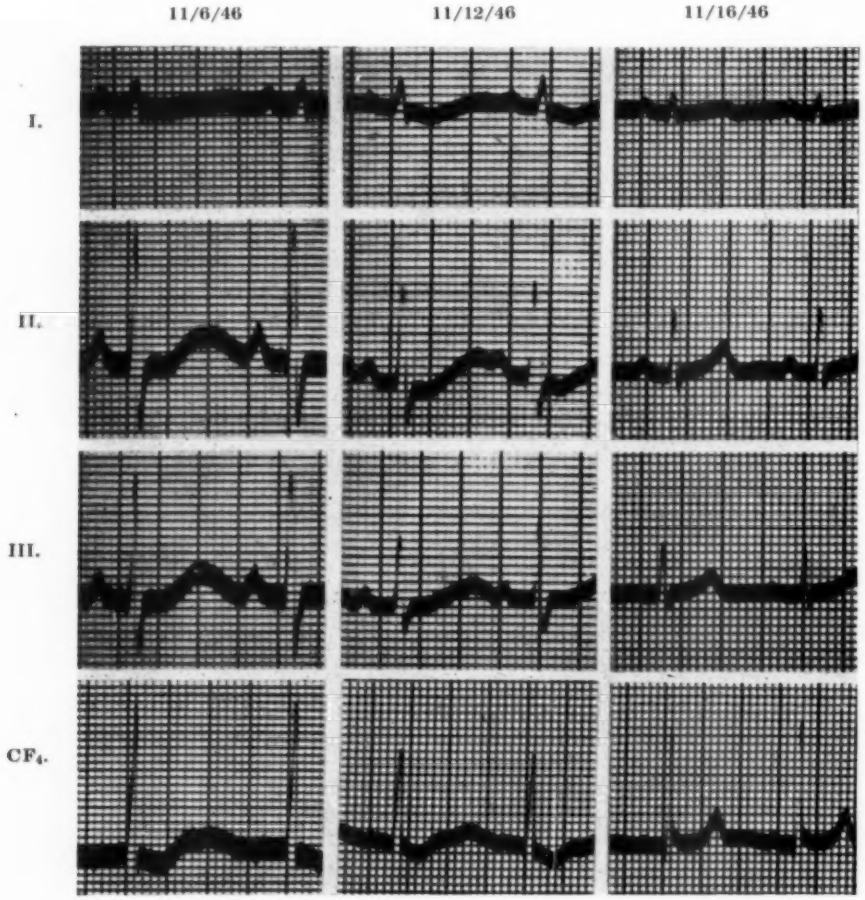


Fig. 6.—Case 6. Hypopotassemia of uncertain cause. The serum potassium content was 3.9 mg. per 100 c.c. on November 12, 10.1 mg. on November 15, and 25.4 mg. on November 17.

On November 13 the patient received 15.0 Gm. of potassium nitrate by mouth, and on November 15, 30.0 Gm. of potassium chloride. The serum potassium content on November 15 was 10.1 mg. per 100 c.c. and on November 17, 25.4 mg. per 100 cubic centimeters. An electrocardiogram on November 16 (Fig. 6) showed sinus rhythm with a rate of 83 per minute. The P-R intervals, QRS complexes, and Q-T intervals were of normal duration. The RS-T segments were no longer depressed in Leads I and II, and the T waves were strikingly different

from those in the earlier records, being of greater amplitude in Lead I, sharply peaked in Leads II, III, and CF_4, and of shorter duration in all leads. No U waves were present in any lead.

Comment: Hypopotassemia in this case caused slight but inconstant prolongation of the QRS complexes, depression of the RS-T segments, and lengthening of the Q-T intervals by unusually broad T waves. In Leads II and III, the T waves were of considerably greater amplitude than in the preceding cases. Comparison of the limb leads with Lead CF_4 suggested that the increased duration of the T waves in the former leads was due in part to fusion of the T waves with U waves. That all of the changes were related causally to the low serum potassium content was demonstrated by their prompt disappearance when the hypopotassemia was corrected by the oral administration of potassium salts.

REVIEW OF THE LITERATURE

There are but few earlier reports concerning the effect of hypopotassemia on the electrocardiogram of man. The first observations were made by Stewart, Smith, and Milhorat[4] in a study of a patient with familial periodic paralysis. In addition to prolongation of the Q-T interval and changes in the form of the T wave similar to those recorded in the present investigation, there was increased duration of the P-R interval and QRS complexes and alteration of the form of the RS-T segments. Attention was directed to the fact that the lengthening of the Q-T interval differed from the lengthening observed in hypocalcemia, inasmuch as the change in the latter condition is due to increased duration of the isoelectric RS-T segment. This is the only earlier report in which the difference between the electrocardiogram of hypopotassemia and that of hypocalcemia is pointed out.

Electrocardiographic studies in a case of periodic paralysis also were made by Stoll and Nisnewitz.[7] During a moderately severe attack, at which time the serum potassium content was 11.0 mg. per 100 c.c., the P-R interval was 0.28 second and the T waves were flat in Lead I and low, rounded, and broad in Leads II and III. The Q-T interval and duration of the QRS complexes were not measured, but both appear to be slightly prolonged in the published records. The changes disappeared after recovery from the paralysis, and this was found to be true whether the termination of an attack was spontaneous or was induced by the administration of potassium.

Holler[8] described the electrocardiographic changes observed in a case of diabetic acidosis with hypopotassemia. At a time when the serum potassium content was 9.8 mg. per 100 c.c., the electrocardiogram showed depression of the RS-T segments and low T waves in the limb leads. The duration of the Q-T interval cannot be measured in the published tracing because the descending limb of the T wave is interrupted by a P wave. The abnormalities disappeared when the serum potassium concentration was restored to normal.

It is well known that overtreatment of Addison's disease with desoxycorticosterone acetate results in a decrease in the serum potassium content, and a few reports are available in which electrocardiograms have been made during treatment with the drug. Thomson[9] published a series of records which show widening and diminution in amplitude of the T waves and prolongation of the Q-T interval as the serum potassium concentration fell from 31.6 mg. per 100 c.c. to 8.3 milligrams. Currens and White[10] observed flat or slightly inverted

T waves in all the limb leads of two patients with Addison's disease who had developed evidence of congestive heart failure while under treatment with desoxycorticosterone acetate. The Q-T interval was not prolonged in either patient, and there were no measurements of the serum potassium at the time the electrocardiograms were made.

Brown, Currens, and Marchand[11] described the electrocardiographic abnormalities recorded in two patients with muscular paralysis due to chronic nephritis, and attributed the changes to potassium loss. In the first case, partial auriculoventricular block was present, the RS-T segments were depressed, and the T waves were low and broad in all leads. Measurements of the serum potassium content were not made, but the electrocardiogram was normal on the day after administration of potassium chloride. In the second case, the T waves were low in all leads, the RS-T segments were slightly depressed, and a prominent U wave was present in Lead IV F. The serum potassium was not measured during the period of muscular weakness, and potassium salts were not administered.

Rapoport and his associates[12] observed lowered T waves in infants suffering from diarrhea and demonstrated that these changes were corrected by the administration of potassium salts. No electrocardiograms were published.

Ellis[13] recently reported a study of the electrocardiograms of four prisoners of war suffering from severe malnutrition and diarrhea. The published records show changes remarkably similar to those observed in the present investigation, and it seems highly probable, therefore, that the abnormalities were due principally to diminished serum potassium concentration. The most striking and constant changes consisted of prolongation of the Q-T interval, broad, abnormal T waves, and large U waves. Inspection of the tracings shows that the lengthening of the Q-T interval was due to the increased duration of the T waves. In two cases the P-R interval was slightly and inconstantly increased, and in one the duration of the QRS complexes was prolonged. Treatment of the patients with corrective diets and added vitamins resulted in return of the records to normal.

DISCUSSION

The results of the present investigation confirm and extend the earlier observations concerning the effect of hypopotassemia on the electrocardiogram and illustrate the manner in which the changes due to hypopotassemia differ from those associated with hypocalcemia. They demonstrate that the earliest effect of a low serum potassium content consists of rounding and broadening of the T waves. The T waves generally decrease in amplitude also, but this is not always the case. The Q-T interval is frequently prolonged, and whether or not this change occurs is determined entirely by the degree to which the duration of the T waves is increased. The RS-T segments are not lengthened but are often slightly depressed. The duration of the QRS complexes is increased occasionally. Prominent U waves commonly appear in the limb leads and Lead CF_4 and, by partial fusion with the descending limb of the T waves, may cause

further apparent lengthening of the Q-T interval. Although the presence of U waves has been noted in some of the earlier reports, the frequency of their occurrence has not been emphasized heretofore.

It was not possible in the present study to establish a critical level of serum potassium concentration at which the electrocardiographic changes of hypopotassemia appear.

In contrast to the findings in hypopotassemia, the electrocardiographic pattern in hypocalcemia is of a simple nature and consists entirely of prolongation of the Q-T interval due to lengthening of the RS-T segment. The duration of the P-R intervals and QRS complexes is not increased, the RS-T segments remain isoelectric, and the T waves are not altered in contour, amplitude, or duration. Prominent U waves do not occur.

The electrocardiographic findings in hypopotassemia and hypocalcemia are of clinical importance, for their recognition may suggest the presence of a condition that otherwise might not be suspected.

SUMMARY

1. The electrocardiographic findings have been described in a typical case of hypocalcemia and in five cases of hypopotassemia due to various causes.

2. Hypopotassemia is characteristically attended by rounded T waves of increased duration and usually of low amplitude. When the widening of the T waves attains a sufficient degree, prolongation of the Q-T interval results. The RS-T segments are not lengthened but often are slightly depressed. Prominent U waves are commonly present and by partial fusion with the descending limb of the T waves may cause further apparent lengthening of the Q-T interval. The duration of the QRS complexes is occasionally increased.

3. In contrast to the findings in hypopotassemia, the electrocardiographic pattern of hypocalcemia is of a simple nature and consists entirely of prolongation of the Q-T interval due to lengthening of the RS-T segment.

REFERENCES

1. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, J. Clin. Investigation **7**:387, 1929.
2. Barker, P. S., Johnston, F. D., and Wilson, F. N.: The Duration of Systole in Hypocalcemia, Am. Heart J. **14**:82, 1937.
3. Wofford, C. P., and Ernstene, A. C.: The Diagnostic Significance of an Increased Q-T Interval in the Electrocardiogram, Cleveland Clin. Quart. **8**:12, 1941.
4. Stewart, H. J., Smith, J. J., and Milhorat, A. T.: Electrocardiographic and Serum Potassium Changes in Familial Periodic Paralysis, Am. J. M. Sc. **199**:789, 1940.
5. Bazett, H. C.: An Analysis of the Time-Relations of Electrocardiograms, Heart **7**:353, 1920.
6. Ashman, R., and Hull, E.: Essentials of Electrocardiography for the Student and Practitioner of Medicine, ed. 2, New York, 1941, The Macmillan Company.
7. Stoll, B., and Nisnewitz, S.: Electrocardiographic Studies in a Case of Periodic Paralysis, Arch. Int. Med. **67**:755, 1941.

8. Holler, J. W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, J. A. M. A. **131**:1186, 1946.
9. Thomson, W. A. R.: Potassium and the T wave of the Electrocardiogram, Lancet **1**:808, 1939.
10. Currens, J. H., and White, P. D.: Congestive Heart Failure and Electrocardiographic Abnormalities Resulting From Excessive Desoxycorticosterone Acetate Therapy in the Treatment of Addison's Disease, AM. HEART J. **28**:611, 1944.
11. Brown, M. R., Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting From Potassium Loss in Chronic Nephritis, J. A. M. A. **124**:545, 1944.
12. Rapoport, S., Dodd, K., Clark, M., and Syllm, I.: Postacidotic State of Infantile Diarrhea; Symptoms and Chemical Data, Am. J. Dis. Child. **73**:391, 1947.
13. Ellis, L. B.: Electrocardiographic Abnormalities in Severe Malnutrition, Brit. Heart J. **8**:53, 1946.

THE VENTRICULAR COMPLEX IN RIGHT VENTRICULAR HYPERTROPHY AS OBTAINED BY UNIPOLAR PRECORDIAL AND LIMB LEADS

MAURICE SOKOLOW, M.D., AND THOMAS P. LYON, M.D.
SAN FRANCISCO, CALIF.

THE dramatic benefits to be obtained from modern cardiac surgical procedures have, among other things, crystallized the need for a more accurate diagnosis of heart disease. One of the most elusive of these conditions is right ventricular hypertrophy, and more definite criteria for its recognition are greatly needed. Roentgenologists and clinicians have attacked the problem, but the roentgenographic diagnosis of right ventricular hypertrophy is notoriously difficult and radiologists differ in their opinions as to the reliability of the criteria thought to be of diagnostic importance.[1-4] Various authors have described the electrocardiographic pattern of marked right ventricular hypertrophy in the standard limb leads[5-10] and in the precordial leads.[11-15,27] The criteria for the diagnosis of the lesser degrees of right ventricular hypertrophy have not been clearly established in either standard or precordial leads, nor has the frequency of the significant findings been accurately defined. It is the purpose of this paper to describe the patterns seen in sixty cases of right ventricular hypertrophy and to differentiate normal right axis deviation (due to position of the heart) from abnormal right axis deviation (due to right ventricular hypertrophy).

SUBJECTS AND METHODS

Sixty patients (of whom twenty-four, or 40 per cent, were 5 years of age or younger) with right ventricular hypertrophy who suffered from cyanotic congenital cardiac disease, tetralogy of Fallot, mitral stenosis, cor pulmonale, or kyphoscoliotic disease were studied. Tables I and II summarize the types of cases and the age and sex distribution. Of the forty-four patients with congenital cardiac disease, in twenty the diagnosis was proved by surgical intervention, in six by autopsy, and in seven by Diodrast angiocardiography (Table I). The diagnosis in the remainder of the group with congenital cardiac anomalies was made by routine clinical and roentgenographic examination. The diagnosis of right ventricular hypertrophy in patients with chronic asthma and emphysema was based on the clinical manifestations of chronic cor pulmonale with dyspnea

From the Division of Medicine of the University of California Medical School, San Francisco, Calif.

Aided in part by a grant from the Mrs. Albert E. Schwabacher Fund.

Presented in preliminary form before the American Federation of Clinical Research, April, 1947, Chicago, Ill.

and cyanosis, as well as on the demonstration of emphysema by roentgen examination. Clinical and roentgen examination supplemented the physical signs of mitral stenosis in patients with rheumatic disease.

TABLE I. THE CAUSES OF RIGHT VENTRICULAR HYPERTROPHY IN THE PRESENT SERIES OF CASES

Congenital cardiac disease		44
Tetralogy of Fallot	18	
Proved by autopsy	4	
Proved surgically	13	
Proved by Diodrast angiocardiograms	1	
Cor triloculare with right ventricular hypertrophy; autopsy	1	
Overriding aorta or high interventricular septal defect with right ventricular enlargement shown by Diodrast angiocardiogram	6	
Miscellaneous cyanotic congenital cardiac disease with abnormal films of the heart but no Diodrast, surgery, or autopsy	19	
Chronic asthma and emphysema		8
Rheumatic heart disease with mitral stenosis		6
Kyphoscoliosis		1
Pulmonary fibrosis		1
Total cases		60

All of the patients were studied by means of standard limb leads, unipolar limb leads, and unipolar precordial Leads V_1 through V_6. On many of the patients further exploratory leads were taken over the right side of the anterior chest, the right side of the upper abdomen, and the xiphoid. Goldberger's modification[16] of Wilson's central terminal was used for the unipolar leads. On all of the patients routine seven-foot films of the chest were taken and on many of the congenital patients Diodrast angiocardiograms were available.*

TABLE II. RIGHT VENTRICULAR HYPERTROPHY; DISTRIBUTION BY AGE AND SEX IN SIXTY CASES

AGE	MALE	FEMALE
1 mo.–2 yrs.	6	7
2 yrs.–5 yrs.	8	3
5 yrs.–10 yrs.	5	2
10 yrs.–20 yrs.	1	4
20 yrs.–30 yrs.	4	4
30 yrs.–50 yrs.	6	4
50 yrs.–70 yrs.	6	0
Total	36	24

The electrocardiograms were analyzed in tabular form on master sheets, all waves of each record being carefully measured through a magnifying lens, if necessary. The amplitude of upright waves was measured from the upper edge

*An independent study by Dr. E. R. Miller and his associates of the Division of Radiology.

of the base line to the peak of the wave; that of inverted waves, from the lower edge. Calibration corrections were applied, if necessary for standardization (1.0 cm. = 1.0 millivolt). In addition to the usual measurements, particular attention was paid to the voltage of the R and S waves in the precordial and unipolar extremity leads in order to calculate the ratios to be described.

One hundred fifty subjects (healthy nurses, medical students, house staff personnel, and flying personnel of a commercial airline, whose histories, physical examinations, electrocardiograms, and roentgenograms of the chest were within normal limits) were used for comparison. The mean age of the normal subjects was 34.6 years, with a range of 4 to 70 years. Four were under the age of 10 years. A separate group of thirteen normal infants from the well-baby clinic were studied for calculation of the R/S ratios and of the ventricular activation time in view of the observations of Battro and Mendy[18] of an abnormally prominent R wave in Lead V_1 in normal infants.

The differentiation of right ventricular hypertrophy and right bundle branch block was attempted and all cases were excluded from this study in which the electrocardiogram showed an M-shaped complex of the QRS with a prominent R wave and a ventricular activation time exceeding 0.07 second in Lead V_1. This was done to exclude right bundle branch block from the series even though it was appreciated that right ventricular hypertrophy and right bundle branch block could coexist.

RESULTS

Table III summarizes the statistical data obtained in the cases of right ventricular hypertrophy, in the entire normal group, and in subjects with right axis deviation (+80° or more) included in the normal group. Table IV summarizes the criteria obtained from a study of our data for the diagnosis of right ventricular hypertrophy, and Table V summarizes the frequency with which the various electrocardiographic abnormalities were encountered here. It will be seen that abnormalities in voltage and ratios of the R and S waves were the most common abnormalities in the precordial leads.

Voltage of the QRS Complex.—The importance of voltage of the QRS complex is apparent from Table V. No standards of voltage in right ventricular hypertrophy have been published comparable to those of Gubner and Ungerleider[19] in left ventricular hypertrophy.[30] The voltage of the R wave and S wave in the present series can be seen in Table III. The mean height of the R wave in Lead V_1 in the normal subjects was 2.3 mm., whereas the mean height of the R wave in right ventricular hypertrophy in V_1 was 9.6 mm., and thirty-five cases (58 per cent) equalled or exceeded the maximum normal R wave of 7.0 millimeters. The mean depth of the S wave in Lead V_1 was 8.6 mm. in the normal group and 3.1 mm. in the cases of right ventricular hypertrophy, and in thirty of these cases (50 per cent) the S wave was less than 2.0 mm. in V_1. The mean depth of the S wave in V_6 in the normal group was only 0.6 mm. and 6.1 mm. in the cases of right ventricular hypertrophy. In thirty cases (50 per cent) of the latter, the S wave equalled or exceeded the maximum normal of 7.0 mm. in V_5 and/or V_6.

TABLE III. THE VENTRICULAR DEFLECTIONS IN THE UNIPOLAR LIMB AND PRECORDIAL LEADS (MEASUREMENTS IN MILLIMETERS)

LEAD	RIGHT VENTRICULAR HYPERTROPHY (60 CASES)				NORMAL (150 CASES)				NORMAL—RIGHT AXIS DEVIATION (19 CASES)			
	MEAN	ST. DEV.	MIN.	MAX.	MEAN	ST. DEV.	MIN.	MAX.	MEAN	ST. DEV.	MIN.	MAX.
V_1												
Q	0.07	0.25	(0.0	1.0)	0.0	0.0	(0.0	0.0)	0.0	0.0	(0.0	0.0)
R	9.6	7.6	(0.0	28.0)	2.3	1.5	(0.0	7.0)	2.1	1.6	(0.0	7.0)
S	3.1	4.1	(0.0	19.0)	8.6	4.3	(2.0	25.0)	8.4	4.3	(1.5	17.0)
T	−1.09	7.77	(−5.0	+ 5.5)	0.15	1.58	(−4.0	+4.0)	−0.26	1.06	(−1.5	+3.0)
VAT*	0.04	0.06	(0.0	0.08)	0.02	0.007	(0.0	0.03)	0.02	0.008	(0.0	0.03)
V_2												
Q	0.0	0.0	(0.0	0.0)	0.0	0.0	(0.0	0.0)	0.0	0.0	(0.0	0.0)
R	9.4	7.1	(0.5	25.0)	5.9	3.1	(0.0	16.0)	5.9	2.8	(2.0	11.0)
S	10.0	6.5	(0.5	24.0)	12.7	5.3	(0.0	29.0)	15.4	5.0	(4.0	29.0)
T	2.2	6.78	(−6.0	+8.0)	5.2	3.32	(−3.0	+18.0)	4.6	2.34	(+1.5	+11.0)
VAT*	0.03	0.01	(0.0	0.08)	0.025	0.006	(0.0	0.04)	0.024	0.008	(0.015	0.04)
V_3												
Q	0.01	0.07	(0.0	0.5)	0.01	0.06	(0.0	0.5)	0.0	0.0	(0.0	0.0)
R	10.1	7.2	(1.0	33.0)	8.9	4.3	(1.5	26.0)	7.4	2.6	(3.0	13.0)
S	10.2	6.0	(0.5	22.0)	8.8	5.3	(0.0	25.0)	11.3	5.7	(2.0	25.0)
T	2.6	6.85	(−7.0	+10.0)	5.38	2.96	(−2.0	+16.0)	5.18	2.21	(+2.0	+10.0)
VAT*	0.03	0.01	(0.0	0.07)	0.03	0.007	(0.02	0.04)	0.029	0.007	(0.015	0.04)
V_4												
Q	0.15	0.92	(0.0	6.5)	0.1	0.4	(0.0	3.0)	0.03	0.02	(0.0	0.5)
R	10.0	7.8	(1.0	35.0)	14.2	5.5	(4.0	27.0)	13.4	4.4	(4.0	23.0)
S	10.4	6.3	(1.0	23.0)	5.2	4.0	(0.0	20.0)	6.5	5.0	(0.0	19.0)
T	2.7	6.84	(−9.5	+11.0)	4.8	2.76	(0.0	+17.0)	4.18	1.79	(+1.0	+8.0)
VAT*	0.03	0.01	(0.0	0.05)	0.034	0.007	(0.02	0.05)	0.032	0.007	(0.02	0.04)

V_5												
	Q	0.31	0.98	(0.0	6.0)	0.3	0.6	(0.0	3.0)	0.2	0.1	(0.0	1.0)
	R	7.9	6.1	(5.0	31.0)	12.1	4.4	(4.0	26.0)	10.2	3.7	(4.0	20.0)
	S	8.5	5.6	(0.5	30.0)	1.5	1.5	(0.0	6.0)	2.0	1.8	(0.0	6.0)
	T	2.4	7.33	(−9.0	+10.0)	3.43	1.62	(0.0	+9.0)	3.29	1.49	(+2.0	+8.0)
	VAT*	0.03	0.01	(0.0	0.05)	0.04	0.01	(0.0	0.05)	0.03	0.008	(0.02	0.04)
V_6												
	Q	0.4	1.1	(0.0	6.5)	0.4	0.5	(0.0	2.0)	0.3	0.2	(0.0	2.0)
	R	6.6	6.1	(0.5	32.0)	9.2	3.6	(4.0	22.0)	8.1	3.6	(2.5	16.0)
	S	6.1	4.8	(0.0	28.0)	0.6	1.0	(0.0	7.0)	0.8	0.9	(0.0	3.5)
	T	2.2	7.89	(−1.0	+12.0)	2.43	1.11	(−0.5	+5.0)	2.37	1.01	(+1.5	+5.0)
	VAT*	0.03	0.01	(0.0	0.05)	0.04	0.01	(0.02	0.05)	0.03	0.01	(0.02	0.05)
aV_L												
	Q	0.28	0.81	(0.0	4.0)	0.2	0.5	(0.0	3.5)	0.1	0.2	(0.0	3.5)
	R	2.7	2.7	(0.0	10.0)	2.1	2.1	(0.0	10.0)	0.9	0.8	(0.0	3.0)
	S	6.0	3.6	(0.0	14.0)	0.4	3.9	(0.0	18.0)	0.5	3.6	(0.0	18.0)
	T	0.3	8.73	(−3.0	+2.5)	0.53	1.26	(−4.0	+6.0)	0.45	1.0	(−2.0	+2.0)
aV_R												
	Q	2.1	2.5	(0.0	9.0)	2.0	3.7	(0.0	8.0)	1.8	2.7	(0.0	8.0)
	R	3.9	2.9	(0.0	14.0)	0.8	0.9	(0.0	5.0)	0.8	0.8	(0.0	3.5)
	S	1.5	2.8	(0.0	12.0)	4.3	4.0	(0.0	13.0)	4.3	4.6	(0.0	13.0)
	T	−1.8	8.78	(−4.0	0.0)	−2.31	0.92	(−5.0	+1.5)	−2.08	0.84	(−4.0	−1.0)
aV_F												
	Q	0.36	0.66	(0.0	3.0)	0.5	1.4	(0.0	3.0)	0.7	0.2	(0.0	2.0)
	R	3.9	2.9	(0.0	14.0)	1.3	8.3	(0.0	20.0)	10.5	4.2	(0.7	20.0)
	S	1.5	2.8	(0.0	12.0)	0.2	1.3	(0.0	8.0)	0.4	2.1	(0.0	2.0)
	T	1.3	8.47	(−2.5	+5.0)	1.86	1.1	(−0.5	+5.0)	1.84	0.96	(+0.5	+4.0)

*Ventricular activation time in seconds; measured from the beginning of the QRS complex to the peak of the R wave.

TABLE IV. THE CRITERIA FOR THE DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY AS OBTAINED BY A STUDY OF SIXTY CASES

I. Voltage of the R and S waves and various ratios:
   1. The R wave in V_1 is 7.0 mm. or more.
   2. The S wave in V_1 is less than 2.0 millimeters.
   3. The S wave in V_5 or V_6 is 7.0 mm. or more.
   4. The sum of the amplitudes of the R wave in V_1 and the S wave in V_5 and V_6 exceeds 10.5 mm. in individuals over 5 years of age.
   5. The R wave in V_5 or V_6 is less than 5.0 millimeters.
   6. The ratio of the R to the S wave in V_5 or V_6 is 1.0 or less.
   7. The R wave in aV_R is 5.0 mm. or more.
   8. The ratio of $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ is 0.4 or less.
   9. The ratio of the R wave in V_1 to the S wave in V_1 exceeds 4.0 in individuals under the age of 5.
   10. The ratio of the R wave to the S wave in V_1 exceeds 1.0 in individuals over the age of 5 years.

II. Delayed onset of the intrinsicoid deflection (delayed ventricular activation time) 0.04 to 0.07 second in V_1 and/or V_2.

III. Depression of the RS-T segment and inversion of the T wave in:
   a. V_1, less often V_2 and V_3 when the R wave equals or exceeds 5.0 millimeters.
   b. aV_L or aV_F when the R wave equals or exceeds 5.0 millimeters.

IV. Marked right axis deviation, greater than +110° suggests, but is not in itself diagnostic of, right ventricular hypertrophy.

The mean height of the R wave in V_5 in the normal group was 12.1 mm., as contrasted to 7.9 mm. in the cases of right ventricular hypertrophy, and in twenty-one cases (36 per cent), the R wave was 4.0 mm. or less. The mean height of the R wave in aV_R was 0.8 mm. in the normal subjects and 3.9 mm. in the cases of right ventricular hypertrophy. Of the latter, the voltage of the R wave in aV_R equalled or exceeded the maximum normal of 5.0 mm. in eighteen cases (30 per cent).

In addition to the absolute value of the height of the R wave and depth of the S wave, the relationship of the R wave to the S wave in V_1 and in V_5 and V_6 was found to be quite different in the group with right ventricular hypertrophy, as compared with the normal subjects (Table VI). Calculations of the R/S ratio in Lead V_5 from data on nine cases of chronic pulmonary heart disease from the paper by Salazar and Sodi-Pallares[20] revealed a mean R/S ratio of 0.94. In six of the nine cases, the R/S ratio in V_5 was less than 0.6, in contrast to the minimum normal in our series of 1.0. The difference between the two groups was more strikingly evident when the ratio of $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ was determined (Table VII). The mean figure for this latter ratio was 1.6 in the cases of right ventricular hypertrophy, as compared with 32 in the normal subjects. In fifteen (48 per cent)

of the thirty-one cases of right ventricular hypertrophy in which the ratio could be calculated, the ratio $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ equalled or was less than the minimum normal value of 0.4. The sum of the total right ventricular potentials R wave in V_1

TABLE V. THE FREQUENCY OF VARIOUS ABNORMALITIES OF THE VENTRICULAR COMPLEX IN RIGHT VENTRICULAR HYPERTROPHY

I.	Voltage of the R and S waves	53
	R wave in V_1, 7.0 mm. or more	35
	S wave in V_1, less than 2.0 mm.	30
	S wave in V_5 or V_6, 7.0 mm. or more	30
	R in V_1 + S in V_5 exceeds 10.5 mm. in individuals over 5 years	26
	R wave in V_5 or V_6, 4.0 mm. or less	21
	R/S ratio, 1.0 or less in V_5 or V_6	19
	R wave in aV_R is 5.0 mm. or more	18
	The ratio* $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ is 0.04 or less	15
	The R/S ratio* exceeds 4.0 in patients under 5 years	9
	The R/S ratio* exceeds 1.0 in patients over 5 years	8
II.	Delayed onset of the intrinsicoid deflection (right ventricular activation time), 0.04 second to 0.07 second	42
III.	Axis deviation between +110° and −80°	37
IV.	Abnormalities of the RS-T segment and T wave	30
	Inverted T wave in V_1 with R wave 5.0 mm. or more	26
	Inverted T wave in V_1, V_2, and V_3	9
	Inverted T wave in V_1 and V_2	6
	Inverted T wave in standard Leads II and III	6
	Inverted T wave in Lead aV_L when associated with R wave greater than 5.0 mm.	4
V.	Tall P waves (greater than 2.5 mm.) in standard Leads II and III or unipolar Leads V_5, V_6, or aV_F	9

*These ratios can be calculated only when R and S waves are both present.

TABLE VI. THE R/S RATIO IN RIGHT VENTRICULAR HYPERTROPHY AS COMPARED WITH NORMAL SUBJECTS

LEAD	NORMAL				RIGHT VENTRICULAR HYPERTROPHY			
	MEAN	ST. DEV.	MIN.	MAX.	MEAN	ST. DEV.	MIN.	MAX.
V_1	0.3	0.3	(0.0	1.0)	3.1	6.3	(0.0	28.0)
V_2	0.2	1.2	(0.1	13.0)	2.1	3.1	(0.0	16.0)
V_3	1.4	1.4	(0.1	10.0)	1.9	2.4	(0.0	12.0)
V_4	4.1	3.8	(0.2	19.0)	1.6	1.7	(0.1	7.0)
V_5	7.3	4.7	(1.0	24.0)	1.4	2.4	(0.1	16.0)
V_6	9.0	5.0	(2.3	22.0)	2.1	4.5	(0.0	28.0)

TABLE VII. THE R/S IN V_5 DIVIDED BY THE R/S RATIO IN V_1 IN CASES OF RIGHT VENTRICULAR HYPERTROPHY AS COMPARED WITH NORMAL SUBJECTS

	$\frac{\text{R/S IN } V_5}{\text{R/S IN } V_1}$			
	MEAN	ST. DEV.	MIN.	MAX.
Right ventricular hypertrophy	1.61	2.26	(0.01	8.5)
Normal subjects	32.0	26.9	(0.4	100.0)

+ S wave in V_5 or S wave in V_6 proved to be significant (Table VIII). The mean sum of the amplitude of R in V_1 + S in V_5 or S in V_6 in the cases of right ventricular hypertrophy was 16.1 mm., as compared with a value of 3.7 mm. in the normal adult subjects. In twenty-six cases (out of thirty-six) of right ventricular hypertrophy over the age of five years, the sum exceeded the maximum normal value of 10.5 millimeters. In two normal children, both 5 years of age, the sum of R in V_1 plus S in V_5 equalled 15 millimeters. In only three normal subjects over the age of 5 did the sum of R in V_1 plus S in V_5 exceed 7.0 millimeters.

TABLE VIII. THE SUM OF THE AMPLITUDES OF THE R WAVE IN S_1 AND THE S WAVE IN S_5 OR V_6 (WHICHEVER IS GREATER) IN CASES OF RIGHT VENTRICULAR HYPERTROPHY AS COMPARED WITH NORMAL SUBJECTS

	R WAVE IN V_1 + S WAVE IN V_5 OR S WAVE IN V_6			
	MEAN	ST. DEV.	MIN.	MAX.
Right ventricular hypertrophy	16.1	9.0	(4.0	37.0)
Normal subjects	3.7	2.4	(0.0	10.5)

In four cases of chronic cor pulmonale with normal voltage of the R wave and normal ventricular activation time in V_1, but with an abnormal R/S ratio in V_5, the sums equalled 11, 12, 13, and 14 mm., respectively (Fig. 7). A calculation of the total right ventricular potential from the data presented on twelve cases of chronic cor pulmonale published by Salazar and Sodi-Pallares[20] revealed that in four (30 per cent) the sum of R in V_1 and S in V_5 exceeded our maximum normal value of 10.5 millimeters. These data suggest that the voltage of the right ventricular potentials may be an important associated criterion of right ventricular hypertrophy and may be especially valuable in borderline cases.

The R/S ratio in V_1 in thirteen normal infants under the age of 2 years was determined and found to be conspicuously greater than that seen in the group of older normal subjects, but was never greater than 4. In these normal infants,

the ventricular activation time* in V_1 did not exceed 0.02 second, despite an R/S ratio of 3 or 4. As will be seen later, this is in distinct contrast to the cases of right ventricular hypertrophy, in which an increased ventricular activation time was found in V_1 when the R/S ratio was of this magnitude. The R/S ratio in V_5 and V_6 in the normal infants did not differ significantly from that seen in the normal adults, again in contrast to what was found in the cases of right ventricular hypertrophy.

*Ventricular Activation Time** (time of onset of the intrinsicoid deflection).—The data in Table III indicate that the time of onset of the intrinsicoid deflection in relation to the onset of the QRS complex in Lead V_1 (ventricular activation time) is occasionally of definite value in the diagnosis of right ventricular hypertrophy. In four different series of normal subjects comprising 332 cases,[17,21,22,29] the onset of the intrinsicoid deflection (ventricular activation time) in V_1 was less than 0.04 second. Kossmann and Johnston[21] stated that the time of onset of the intrinsicoid deflection in the normal individual averages 0.02 second in V_1. In the present control series of normal subjects the upper limit of normal found in Lead V_1 was 0.03 second. This is in contrast to the cases of right ventricular hypertrophy of which 42 per cent of the total revealed a ventricular activation time of 0.04 second or more, but less than 0.07 second in V_1. Delay in the ventricular activation time was found in practically all of the proved cases of pulmonary stenosis (Figs. 1, 2, and 4), in some of the cases of mitral stenosis (Fig. 5), but rarely in the cases of chronic cor pulmonale (Fig. 7). In some instances of right ventricular hypertrophy, notching of the upstroke of the R wave occurred in V_1 (Fig. 2) and suggested the presence of an associated conduction defect, but in these cases, the ventricular activation time in V_1 was less than 0.06 second, and broad, slurred S waves in the left precordial leads were absent. The possibility of an associated right bundle branch block was considered when the ventricular activation time in V_1 exceeded 0.07 second; cases of this type have been excluded from this study. The right ventricular activation time may not be delayed in the marked right ventricular hypertrophy of pulmonary stenosis or related lesions if dextrocardia is also present (Fig. 3). In the cyanotic child whose tracing is shown in this figure, the bizarre axis, the abnormalities in the unipolar extremity leads, and the RS ratio in V_6 lead to the correct ante-mortem diagnosis of right ventricular hypertrophy.

RST-T Abnormalities.—In contrast to their frequency in left ventricular hypertrophy, abnormalities of the RS-T segment and T waves in the unipolar precordial and extremity leads were seen less frequently and were of less diagnostic value in right ventricular hypertrophy than the abnormalities of voltage and ventricular activation time. Earlier workers emphasized the importance of a depression of the RS-T segments with inversion of the T waves in Leads II and III in the diagnosis of right ventricular hypertrophy.[5-10] In the cases of the present series, these RST-T changes were seen inconsistently in Leads II and III (Table III). Depression of the RS-T segment and inversion of the T

*The time in seconds from the onset of the QRS complex to the beginning of the abrupt downstroke of the R wave.

waves, when present in the extremity leads, was seen more frequently in the left leg lead (aV_F) and more rarely found in the left arm lead (aV_L) (Figs. 4 and 7). The characteristic RST-T contour of ventricular hypertrophy with depressed convex RS-T segment and asymmetrically inverted T wave was seen more frequently in the right precordial leads than in the extremity leads. When the

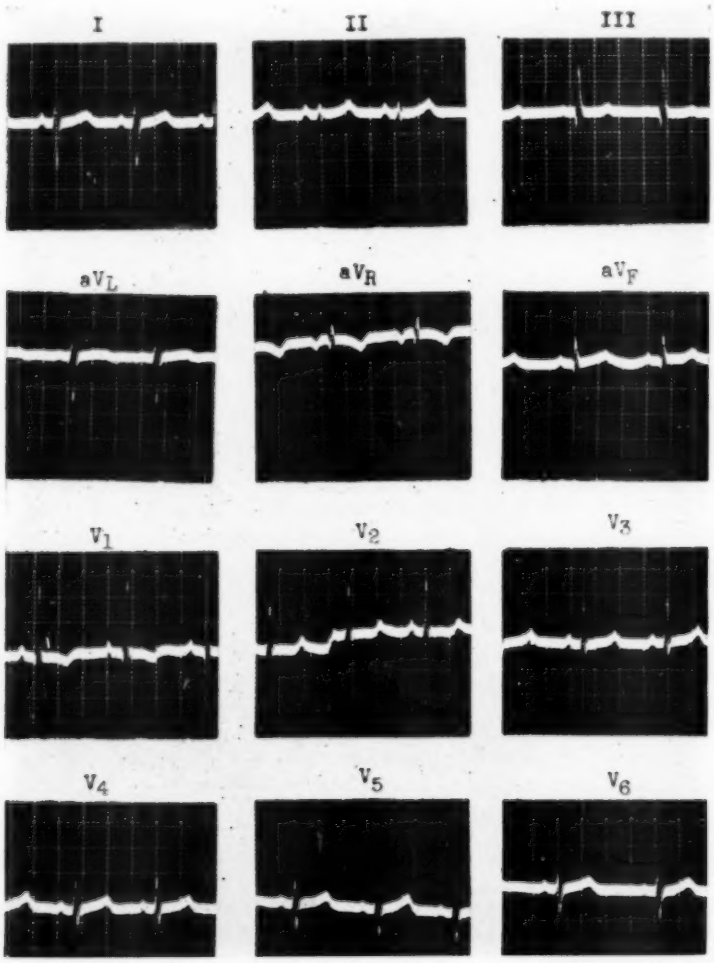


Fig. 1.—S. Z., boy, age 7, U133502. Tetralogy of Fallot. Blalock operation with excellent results. Tracing shows typical finding of right ventricular hypertrophy with marked right axis deviation, tall R wave, absent S wave, delayed ventricular activation time, slightly depressed R-ST segment and inverted T wave in V_1, and small R and deep S wave with short ventricular activation time in V_5 and V_6.

RST-T complex was normal in the standard and extremity leads (Figs. 1 and 2), characteristically tall R waves with delayed ventricular activation time and abnormal RST-T findings occasionally were seen in Leads V_1 and V_2. Inverted T waves in V_1 through V_3 appeared occasionally as the sole electrocardiographic manifestation of acute cor pulmonale (acute pulmonary embolism).

The RST-T abnormalities were first seen either in Lead V_1 or in the unipolar extremity leads. When the left leg lead was abnormal, RST-T abnormalities were usually found in standard Leads II and III (Figs. 4 and 7).

Table IX summarizes the relationship of the T wave to the height of the R wave in patients with right ventricular hypertrophy as compared with the normal subjects.

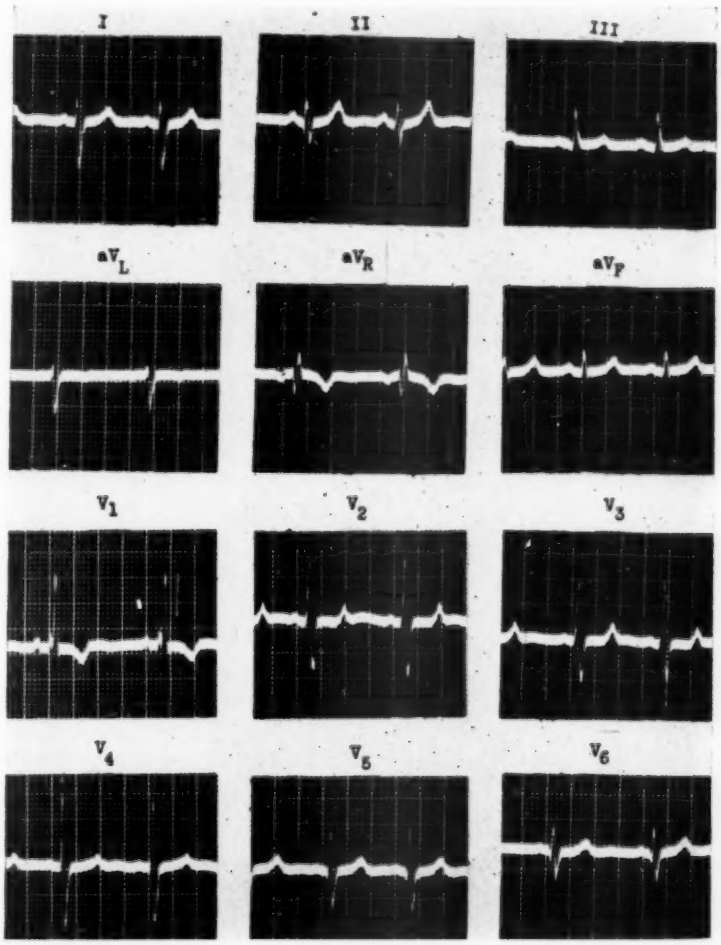


Fig. 2.—F. L., boy, age 7, U132040. Pulmonary atresia with marked right ventricular hypertrophy proved at autopsy. Note the typical findings of right ventricular hypertrophy. Lead V_1 reveals the typical abnormalities, whereas V_2 is not abnormal.

P-Wave Abnormalities.—Abnormalities of the P wave have been noted frequently in right ventricular hypertrophy. Katz[10] has referred to the so-called "P pulmonale pattern" in which large P waves occur in Leads II and III. Salazar and Sodi-Pallares[20] also emphasized the importance of abnormal P waves in Leads II, III, and aV_F in chronic cor pulmonale. Our data (Table V) show the occasional presence of these findings, although we have not diagnosed right ventricular

TABLE IX. THE RATIO OF THE R WAVE TO THE T WAVE (R/T RATIO) IN CASES OF RIGHT VENTRICULAR HYPERTROPHY AS COMPARED WITH NORMAL SUBJECTS

LEAD	NORMAL				RIGHT VENTRICULAR HYPERTROPHY			
	MEAN	ST. DEV.	MIN.	MAX.	MEAN	ST. DEV.	MIN.	MAX.
V_1	1.4	0.9	(0.3	7.0)	3.9	3.1	(0.5	11.0)
V_2	1.4	1.4	(0.2	12.0)	3.3	2.9	(0.2	11.0)
V_3	1.9	1.6	(0.3	13.0)	3.1	2.9	(0.1	15.0)
V_4	2.9	1.7	(0.3	9.0)	3.4	3.3	(0.1	17.5)
V_5	3.5	1.6	(1.0	9.0)	3.0	2.2	(0.6	10.0)
V_6	4.1	1.9	(1.7	10.0)	2.6	1.6	(0.8	7.0)
VL	2.6	1.9	(0.1	10.0)	2.6	2.1	(0.5	8.0)
VF	4.6	3.2	(0.3	14.0)	4.2	2.7	(0.7	10.0)

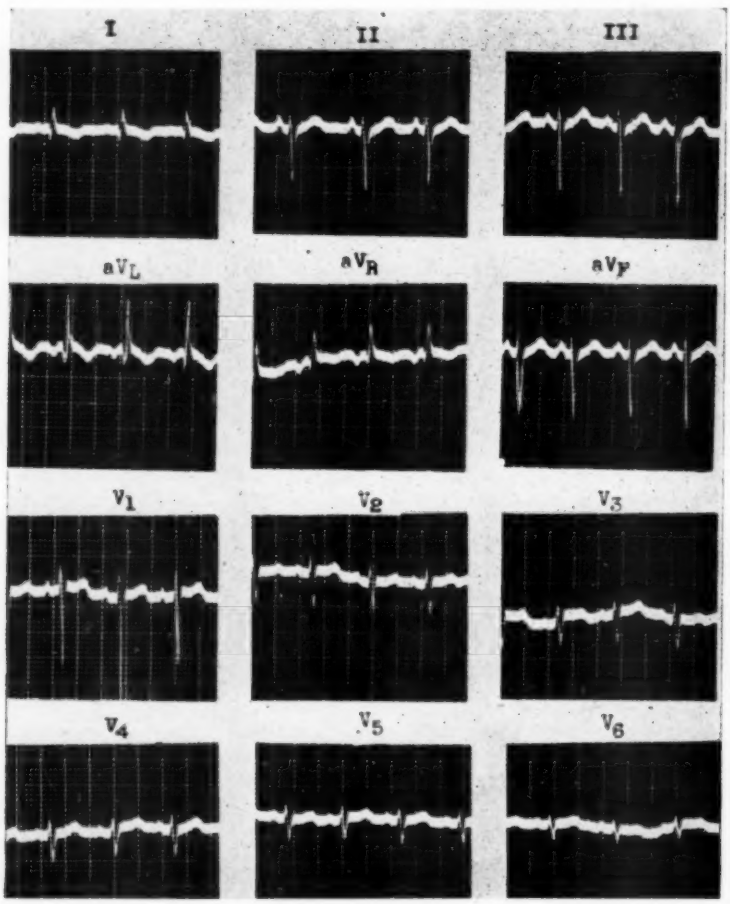


Fig. 3.—R. C., boy, age 10 months, U133966. Hypoplastic pulmonary artery, interauricular septal defect, dextrocardia, and marked right ventricular hypertrophy proved at autopsy. The dextrocardia explains the bizarre axis and absence of typical findings in Lead V_1.

hypertrophy solely on the basis of the P-wave abnormalities, nor do we recommend such a procedure. Tall, peaked P waves, rather than broad, notched P waves were the usual variation from normal seen in both the chronic cor pulmonale group (Figs. 6 and 7) and in the patients with congenital cardiac disease. In mitral stenosis, however, broad or notched P waves were the usual finding (Fig. 5).

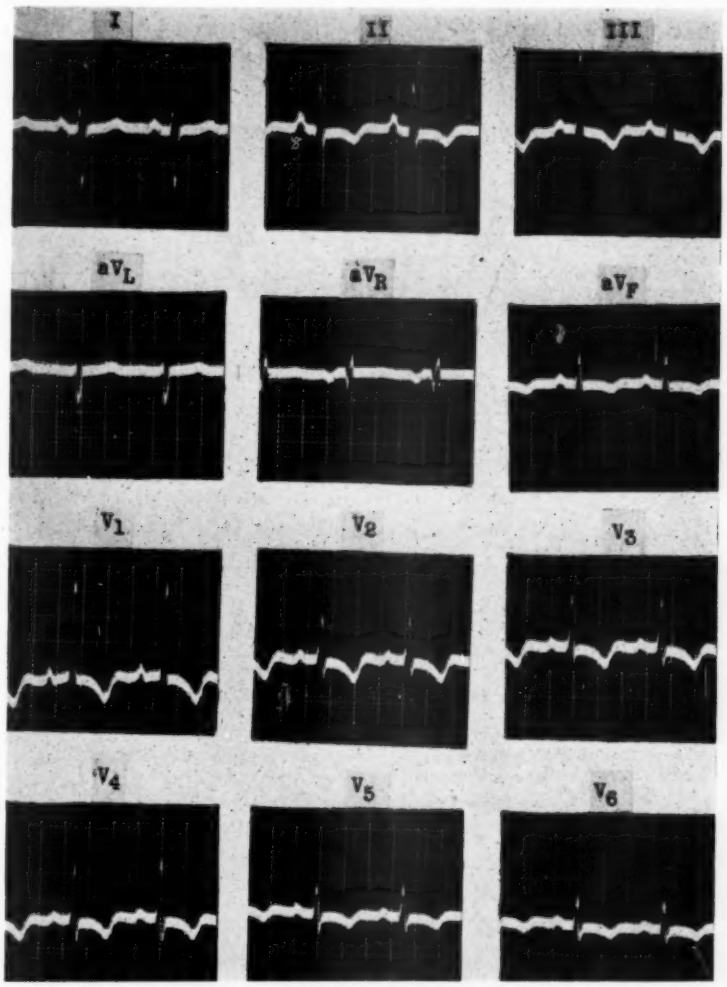


Fig. 4.—L. C., woman, age 25, U134697. Pulmonary stenosis and patent interauricular septal defect with right ventricular hypertrophy proved at autopsy. Right ventricular thickness, 1.5 cm.; left ventricular thickness 1.1 cm. Normal coronary arteries.

Electrocardiographic Position of the Heart.—The electrocardiographic position of the heart, using the criteria of Wilson and his associates,[12] was frequently indeterminate. A horizontal position was noted on occasion, but often neither the right nor the left precordial leads in any way resembled the electrocardiographic patterns of the left leg or the left arm leads. At times, the right pre-

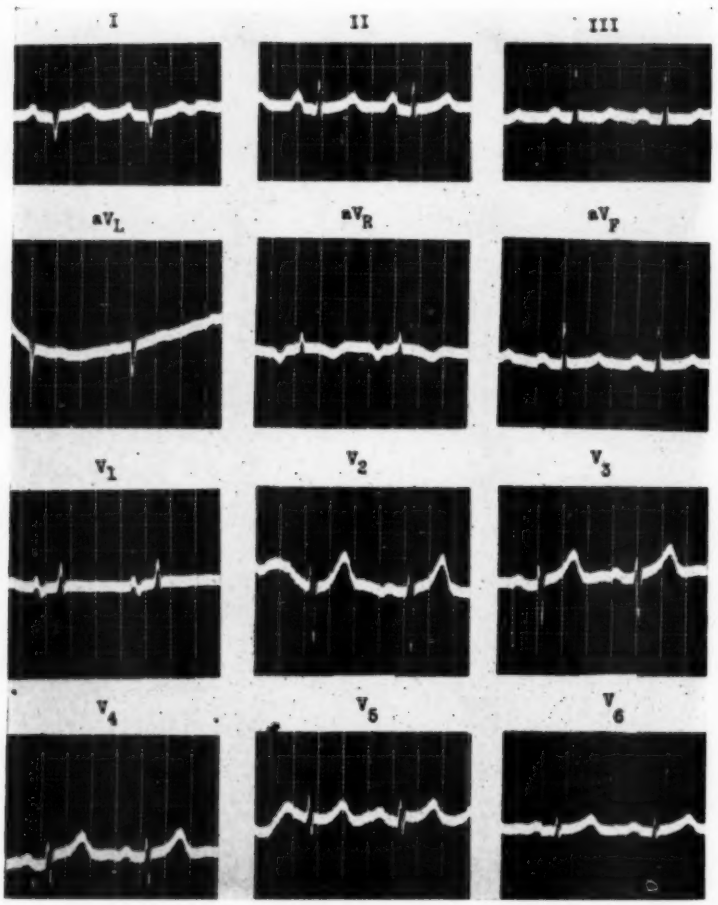


Fig. 5.—G. T., woman, age 29. Mitral stenosis. Note the abnormal P waves in Leads II, III, and aV_F, the monophasic upright R wave in aV_R, the broad negative phase of the P wave in V_1, and the R/S ratio in V_1 with a ventricular activation time of 0.04 second. The R/S ratio in V_1 is definitely abnormal, whereas that in V_2 is quite normal.

cordial leads most closely resembled the pattern seen in the right arm lead, suggesting that rotation of the heart had occurred in such a manner as to allow the right ventricle to face the right arm. Variations in the pattern of right ventricular hypertrophy in the standard leads due to variable position of the heart were seen less frequently than in left ventricular hypertrophy.[30] The electrical axis was calculated according to the method of Carter and his associates[23] and the findings tabulated. It was found that practically all patients with congenital cardiac disease with marked right ventricular hypertrophy had a marked right axis deviation, usually greater than $+120°$, and at times ranging into bizarre axes such as -160 degrees. The axes obtained in the lesser degrees of right ventricular hypertrophy, such as were found in mitral stenosis and chronic cor pulmonale, fell into the range of the upper limits of normal, so that axis deviations of $+80°$ to $+110°$ were noted frequently in these cases.

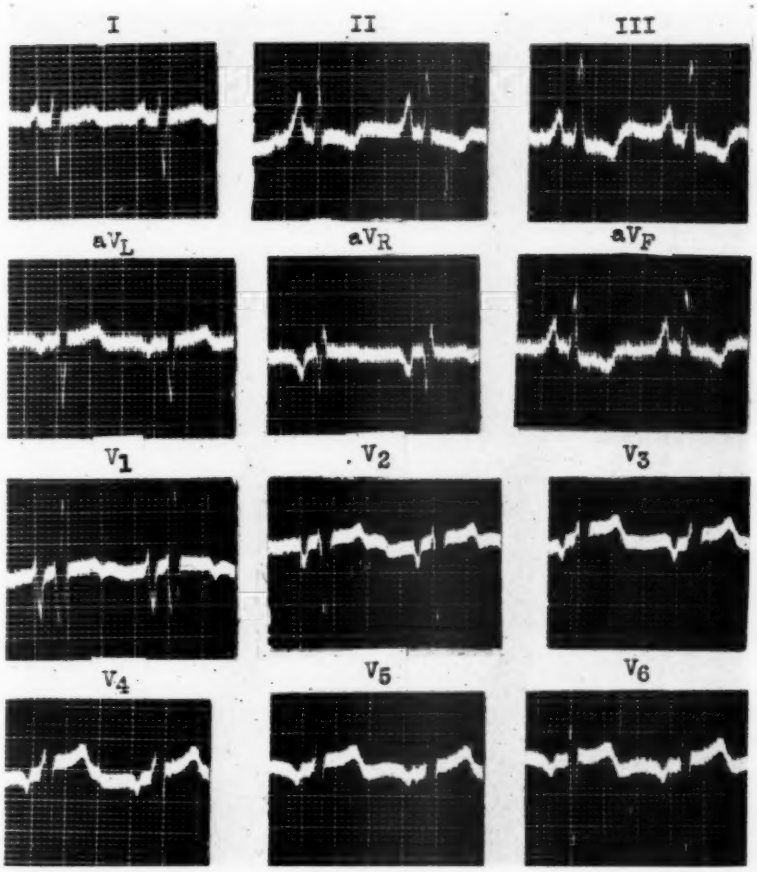


Fig. 6 (Courtesy of Dr. Mervin J. Goldman, Veterans Administration Hospital, Oakland, Calif.).—V. H. S., a man, age 60. Increasing cough, sputum, and dyspnea for twelve years. On admission, right heart failure. Autopsy showed diffuse pulmonary fibrosis, emphysema, and bronchiolectasis. Right ventricular wall, 10 mm; left ventricular wall, 10 mm.; heart weight, 460 grams.

DISCUSSION

It is apparent that the electrocardiographic findings are reliable and consistent in the well-marked case of right ventricular hypertrophy such as occurs in pulmonary stenosis or tetralogy of Fallot (Figs. 1, 2, and 4). Such hypertrophy can be strongly suspected if the electrical axis in the standard limb leads is greater than +110 degrees. Definitive criteria, however, required a study of Leads V_1, V_5, and occasionally aV_R. Abnormal findings in Lead aV_R were rarely observed unless diagnostic changes were also seen in Leads V_1 and/or V_5. In the eighteen cases of congenital cardiac disease verified at surgery or autopsy, all had the typical findings of right ventricular hypertrophy in Leads V_1, V_5, and aV_R (Figs. 1, 2, and 5).

The differentiation of normal from abnormal right axis deviation is of clinical importance and cannot reliably be made from the standard leads alone, even

though the electrical axis is greater than +110°, and abnormalities of the RS-T segment and T waves occur in Leads II and III. The unipolar extremity leads have proved of value in this differentiation by indicating a normal vertical position of the heart to explain the right axis deviation (Fig. 8). However, when individuals with cardiac lesions, such as mitral stenosis, were found to have vertically placed hearts and right axis deviation, further study was required with unipolar precordial and limb leads to determine whether the axis deviation was

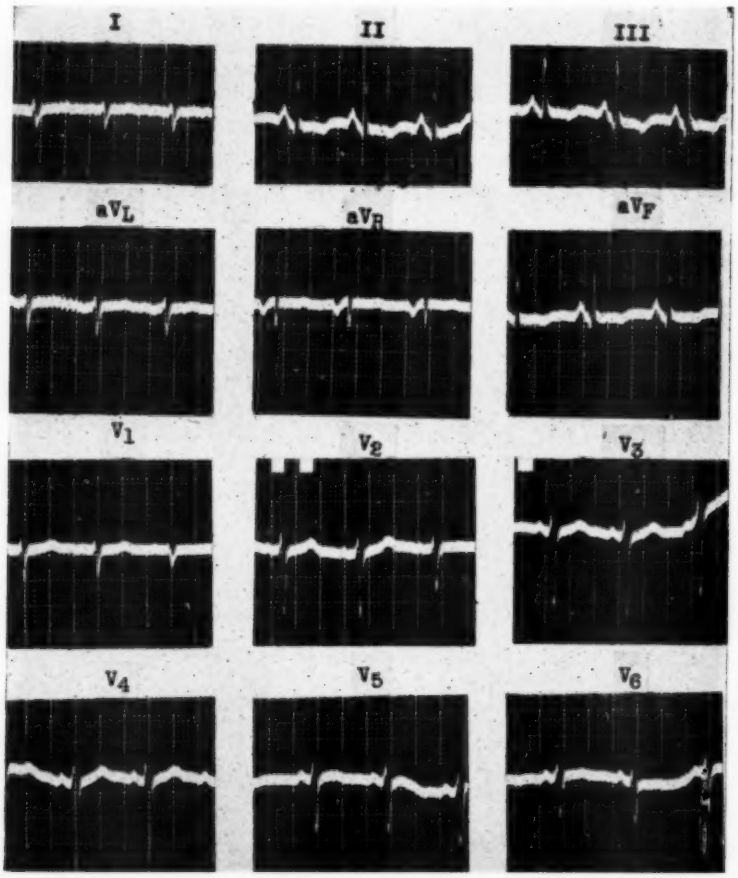


Fig. 7.—W. D., man, age 34, U134878. Chronic asthma, emphysema, and cor pulmonale. Note the abnormal RST-T complex in Leads aVF, II, and III with the low, upright T wave in aVR. The very small R in V_5 and V_6 with a deep S wave in these leads is abnormal. The R wave in V_1 plus the S in V_5 equals 11 millimeters.

due to right ventricular hypertrophy or to a vertical heart with a clockwise rotation on its longitudinal axis. The precordial leads were most helpful in this situation since none of the findings characteristic of right ventricular hypertrophy were observed in these leads in normal subjects with vertical hearts and right axis deviation. Leads V_1 and V_5 were of especial value, and from the changes in these leads the diagnosis was made in most cases. The importance of establishing the diagnosis of right ventricular hypertrophy in individuals with cardiac

lesions which put a strain on the right side of the heart is clear. As Katz[10] stated: "The presence of right ventricular hypertrophy indicates that an acoustically evident valvular lesion has become dynamically important." The prognosis is therefore less favorable.

It is not clear why the predominant features of right ventricular hypertrophy should often be seen solely in Lead V_1 and less often in V_2 as well (Figs. 1, 2, and 5) since the clockwise rotation of the heart in right ventricular hypertrophy

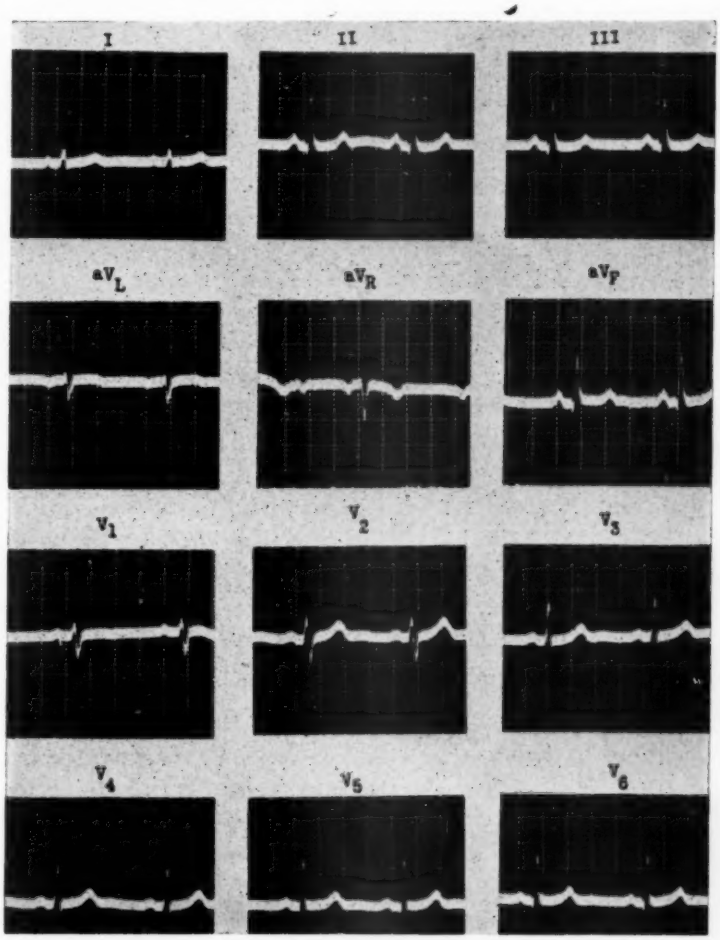


Fig. 8.—B. P., woman, age 22, U111442. Axis +85. Normal vertical heart.

allows the right ventricle to present as the major portion of the anterior cardiac surface. But in precordial Positions 3 and 4, despite the fact that the exploring electrode is presumably over the right ventricle, patterns similar to those from the left ventricle have been obtained (Fig. 2). This is of practical importance because some clinics utilize Position 2 as the site for recording the routine right precordial lead. If right ventricular hypertrophy is suspected, Lead V_1 should

be taken, because often V_2 is not abnormal (Fig. 2) and the diagnosis of right ventricular hypertrophy would then be dependent largely on the changes in V_5 and V_6, leads which give signs of lesser reliability (Figs. 6 and 7).

A study of the electrocardiographic position of the heart has revealed errors in the diagnosis of ventricular hypertrophy. Earlier authors have described the combination of right axis deviation and inverted T wave in standard Leads II and III as typical of right ventricular hypertrophy.[5-10] However, we have noted cases of *left* ventricular hypertrophy in vertical hearts, where the same combination of findings may be present in the standard limb leads (Fig. 9). This fact has been described clearly by Wilson and his associates,[12] but apparently has not been sufficiently appreciated. Study of the precordial leads in these cases will reveal the changes in V_5 and V_6 as being the result of left and not right ventricular hypertrophy, and the left leg lead will show the findings seen in left ventricular hypertrophy. Since the abnormal RST-T changes appear in Lead aV_F, they usually also appear in Leads II and III. In occasional cases, the RS-T abnormalities may appear only in Lead aV_F. The right axis deviation is due to the vertical position of the heart. Left ventricular hypertrophy can be suspected in these circumstances because the S wave in Lead I may be small or absent and the R wave is usually tall in Leads II and III (Fig. 9). The precordial leads, however, are required for the definitive diagnosis.[30]

The frequency of right ventricular hypertrophy in chronic pulmonary disease (as determined by autopsy) has been stressed,[24,25,26] and yet the clinical diagnosis of right ventricular hypertrophy has been difficult to establish. Our results suggest that calculation of the various ratios and reference to the data on voltage presented may be helpful in diagnosis. Salazar and Sodi-Pallares[20] in a recent study of fourteen cases of chronic pulmonary heart disease have commented on the frequency of normal findings in Leads V_1 and V_2 in this group of cases and the fact that reliance for diagnosis must be placed on abnormalities found in Leads V_5 and V_6 and on the abnormal P-wave pattern. Care must be taken that precordial leads are taken sufficiently far to the left in order to be well past the transitional zone before a small R and prominent S wave in Leads V_5 or V_6 are interpreted as supportive evidence for right ventricular hypertrophy. In patients with marked clockwise rotation of the heart, a prominent S wave may be present over a transitional zone which occasionally is displaced as far to the left as Position 6 or rarely 7. A small R wave may be found over the fringes of a myocardial infarct, but here a deep S wave is rarely seen.

Further study is required in infants and in cases of early right ventricular hypertrophy due to cor pulmonale and mitral stenosis in order to establish the reliability of these criteria when the variations from normal occur solely in the left precordial leads.

Myers and his associates[28] have published very recently an excellent paper on the electrocardiographic criteria of right ventricular hypertrophy based on forty autopsied cases. This paper appeared just as the final draft on our paper was being prepared. Myers and his associates emphasized the importance of the R/S ratios in the right and left precordial leads, the ventricular activation time,

the inversion of the T wave in Lead V_1, and the fact that incomplete or complete right bundle branch block may be associated with right ventricular hypertrophy. They noted the need for considering the possibility of abnormal displacement of the transitional zone to the right or to the left before attributing the findings to hypertrophy of the right ventricle. They also emphasized the relative diagnostic inadequacy of the pattern of a depressed RS-T segment in Leads II and III and inversion of the T wave in these leads, findings that for so long have been considered the basic pattern for right ventricular hypertrophy.

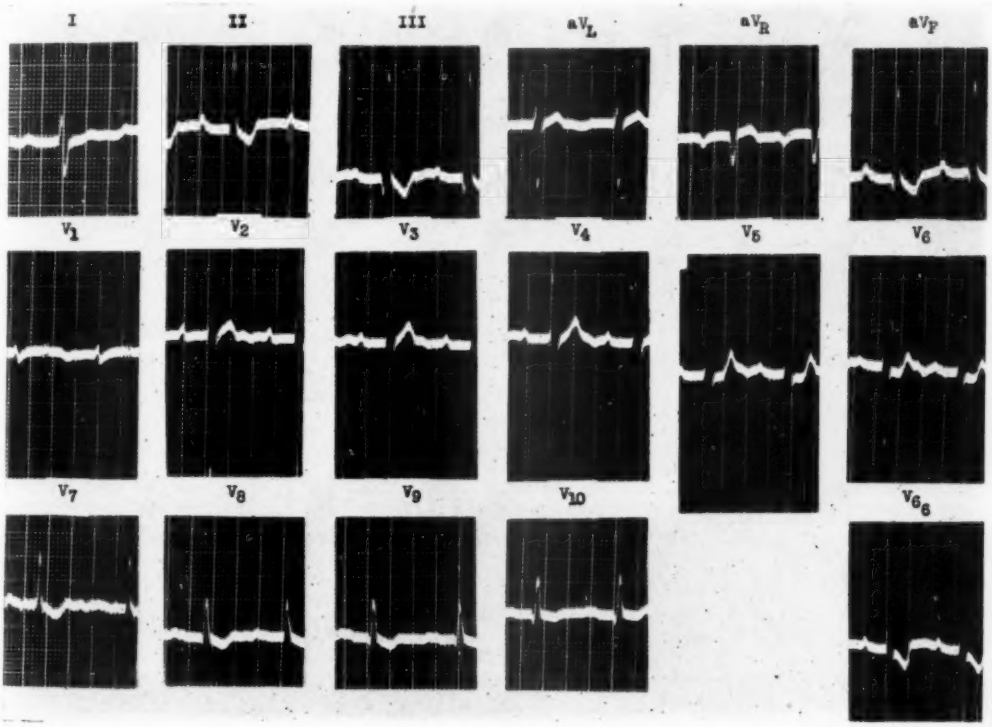


Fig. 9.—M. S., a woman, age 30. Congenital heart disease with large pulmonary artery and left ventricular hypertrophy confirmed by Diodrast angiocardiogram. Right axis deviation with inverted T_2 and T_3 plus the deep S in V_6 suggested right ventricular hypertrophy, but the abnormalities in aV_F indicated the need for further left precordial exploratory leads. Leads V_7 to V_{10} and V_6 in the sixth intercostal space indicated left ventricular hypertrophy with displacement of the transitional zone to Position 7.

The detailed data given by Myers and his associates on forty autopsied cases with right ventricular hypertrophy in Table II of their paper[28] were used to determine the reliability of the criteria which we have compounded from a study of our sixty cases. Of the thirty-three cases in Groups A through E of their classification, all would have been diagnosed as right ventricular hypertrophy by our criteria. Of the seven cases in Group F which were not diagnosed as right ventricular hypertrophy ante mortem by Myers and his associates, Case 37

would have been diagnosed right ventricular hypertrophy according to our criteria. The reliability of our diagnostic criteria when applied to Myers' autopsied cases is demonstrated by the analysis summarized in Table X.

TABLE X. THE FREQUENCY OF VARIOUS ABNORMALITIES OF VOLTAGE OF THE VENTRICULAR COMPLEX IN RIGHT VENTRICULAR HYPERTROPHY CALCULATED FROM DATA PUBLISHED ON FORTY AUTOPSIED CASES BY MYERS AND HIS ASSOCIATES,[25] AND COMPARED WITH THE PRESENT SERIES OF SIXTY CASES

VOLTAGE OF THE R AND S WAVES	FREQUENCY			
	MYERS ET AL. (40 CASES)		SOKOLOW AND LYON (60 CASES)	
	NO.	PER CENT	NO.	PER CENT
R wave in V_5 or V_6 4.0 mm. or less	18	45	21	35
R wave in V_1 7.0 mm. or more	15	38	35	58
S wave in V_1 less than 2.0 mm.	13	33	30	50
S wave in V_5 or V_6 7.0 mm. or more	13	33	30	50
R wave in V_1 + S wave in V_5 exceeds 10.5 mm.	8	20	26	43
R/S ratio 1.0 or less in V_5 or V_6	11	28	19	32
R wave in aV_R 5.0 mm. or more	9	23	18	30
The ratio $\frac{\text{R/S wave in } V_5}{\text{R/S wave in } V_1}$ is less than 0.4	11	28	15	25

CONCLUSION AND SUMMARY

1. An analysis of the electrocardiographic patterns as obtained by unipolar leads in sixty cases of right ventricular hypertrophy is presented and compared with the findings in 150 normal subjects.

2. The typical electrocardiographic pattern of right ventricular hypertrophy, as seen in the tetralogy of Fallot, consists of a tall R wave, a small to absent S wave, and delayed intrinsicoid deflection (delayed ventricular activation time) in the right precordial leads, especially V_1; a small R and prominent S wave with a small R/S ratio in the left precordial Leads V_5 and V_6; a prominent R wave in aV_R; the RS-T segment may be depressed and T wave inverted in Lead V_1 or V_2; similar RST-T changes may occur in Lead aV_L or aV_F and Leads II and III, but these changes are inconsistent; and the standard leads may show right axis deviation or marked left axis deviation if unusual rotation has occurred.

3. Any of the changes noted in (2) may be absent or less strikingly abnormal when seen in the early development of the pattern of right ventricular hypertrophy. This occurs most typically in cases of mitral stenosis and cor pulmonale.

4. The R/S ratio in Lead V_1 exceeded the maximum normal value of 1.0 in adults in forty-three (72 per cent) of the cases of right ventricular hypertrophy; the R/S ratio in Leads V_5 or V_6 was less than the minimum normal value of 1.0 in nineteen (32 per cent) of the cases of right ventricular hypertrophy. Calculation of these ratios was thus very helpful in the diagnosis of right ventricular hypertrophy.

5. The R/S ratio in Lead V_5 divided by the R/S ratio in V_1 was less than the minimum normal value of 0.4 in fifteen (48 per cent) of the cases of right ventricular hypertrophy in which the ratio could be calculated.

6. The maximum normal height of the R wave of 7.0 mm. in V_1 was exceeded in thirty-five (58 per cent) of the cases of right ventricular hypertrophy.

7. The sum of the total right ventricular potentials (the height of the R wave in Lead V_1 plus the depth of the S wave in Lead V_5 or V_6) in twenty-six of thirty-six cases of right ventricular hypertrophy exceeded the maximum normal value of 10.5 mm. in adults.

8. In chronic cor pulmonale, diagnosed clinically, the only electrocardiographic abnormality may be a small R wave in Lead V_5 or V_6 accompanied by a prominent S wave and a small R/S ratio in these leads. The findings in these leads were similar to those obtained in the same leads in definite right ventricular hypertrophy (as in pulmonary stenosis) and differ from the findings in normal vertical hearts. Such findings, therefore, should permit one to suspect, but not definitely diagnose, right ventricular hypertrophy. In four cases of chronic cor pulmonale in which a small R/S ratio in Leads V_5 and V_6 represented the only abnormal findings, the sum of the R wave in V_1 and the S wave in V_5 exceeded the maximum normal of 10.5 mm. and, therefore, the suspicion of the presence of right ventricular hypertrophy was strengthened.

9. Unipolar precordial leads may differentiate normal from abnormal right axis deviation by demonstrating either the normal pattern or that of right ventricular hypertrophy. The patterns obtained in unipolar precordial leads in cases of normal vertical hearts with right axis deviation of $+80°$ or more do not differ from the findings obtained by similar leads in normal intermediate or horizontal hearts.

10. Unipolar precordial leads in infants were characterized by a greater R/S ratio in Leads V_1 and V_2 than is seen in older individuals; these infants do not, in a limited study, show the delayed intrinsic deflection in Leads V_1 and V_2 or the altered R/S ratio in V_5 and V_6 that characterizes right ventricular hypertrophy.

11. The electrocardiographic position of the heart could not be determined accurately in many cases of right ventricular hypertrophy because neither the right nor left arm leads resembled either the right or left precordial leads. At times the right precordial leads resembled most closely the right arm lead, suggesting that in addition to the clockwise rotation on the longitudinal axis of the heart characteristic of right ventricular hypertrophy, the right ventricle and anterior portion of the cardiac surface is rotated clockwise around the anteroposterior axis of the heart.

Grateful acknowledgment is made to Miss Nancy Gelardi, Mrs. Doris Tuttle, Mrs. Angelina Galente, and Mrs. Suzanne Cahill for their technical assistance, and to Dr. John C. Talbot for statistical advice.

ADDENDUM

To date we have had eighteen cases in which the electrocardiographic diagnosis of right ventricular hypertrophy was made on the basis of the criteria presented. In seventeen patients the right ventricle was at least 5 mm. thick and in the remaining patient a single ventricle 7 mm. thick was presented.

REFERENCES

1. Parkinson, J., and Hoyle, C.: The Heart in Emphysema, Quart. J. Med. **6**:59, 1937.
2. Rigler, L. G., and Hallock, P.: Chronic Cor Pulmonale, Am. J. Roentgenol. **50**:453, 1943.
3. Sussman, M. L., Grishman, A., and Steinberg, M. F.: The Roentgenologic Diagnosis of Right-sided Enlargement of the Heart, New England J. Med. **228**:777, 1943.
4. Schwedel, J. B.: Clinical Roentgenology of the Heart, New York, 1946, Paul B. Hoeber, Inc., p. 119.
5. Barnes, A. R., and Whitten, M. B.: Study of T Wave Negativity in Predominant Ventricular Strain, Am. Heart J. **5**:14, 1929.
6. Berliner, K., and Master, A. M.: Mitral Stenosis, Arch. Int. Med. **61**:39, 1938.
7. Comeau, W. J., and White, P. D.: The Clinical Significance of Right Axis Deviation in the Electrocardiogram, Am. Heart J. **18**:334, 1939.
8. Eisenberg, G., and Gibson, S.: Congenital Heart Disease and the Electrocardiogram, J. Pediat. **19**:452, 1941.
9. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram Including the Cardiac Arrhythmias, ed. 4, New York, 1941, Paul B. Hoeber, Inc.
10. Katz, L. N.: Electrocardiography, ed. 2, Philadelphia, 1946, Lea & Febiger.
11. Hecht, Hans: Brustwandableitungen in der klinischen Elektrokardiographie, Deutsches Arch. f. kiln. Med. **179**:1, 1936.
12. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944.
13. Sodi-Pallares, C. P.: Nuevas Bases de Electrocardiografias, Edicion del Instituto Nacional de Cardiologia, México, D. F., 1945.
14. Goldberger, E., and Schwartz, S. P.: Electrocardiograms in Chronic Pulmonary Disease, Am. Rev. Tuberc. **53**:34, 1946.
15. Sokolow, M.: Present Concepts of the Clinical Significance of Unipolar Precordial Electrocardiograms, California Med. **65**:151, 1946.
16. Goldberger, E.: A Simple, Indifferent Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented Unipolar Extremity Leads, Am. Heart J. **23**:483, 1942.
17. Sokolow, M., and Friedlander, R. D.: The Normal Unipolar Precordial and Limb Lead Electrocardiogram, Am. Heart J. In press.
18. Battro, A., and Mendy, J. C.: Precordial Leads in Children, Arch. Int. Med. **78**:31, 1946.
19. Gubner, R. S., and Ungerleider, H. E.: Electrocardiographic Criteria of Left Ventricular Hypertrophy, Arch. Int. Med. **72**:196, 1943.
20. Salazar, M. M., and Sodi-Pallares, D.: Estudio Sobre el Corazon Pulmonar Cronico; Analisis de 14 Casos, Arch. Int. Cardio. México **16**:22, 1946.
21. Kossmann, C. E., and Johnston, F. D.: Precordial Electrocardiogram. I. The Potential Variations of the Precordium and the Extremities in Normal Subjects, Am. Heart J. **10**:925, 1935.
22. Sodi-Pallares, D., Paras, O., Cabrera, E., and Mendoza, F.: La Deflexion Intrinseca en Casos Normales y en Hipertrofias Ventriculares, Arch. Inst. Cardiol. México, **16**:397, 1946.
23. Carter, E. P., Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, Bull. Johns Hopkins Hosp. **30**:162, 1919.
24. Kountz, W. B., Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, Am. Heart J. **11**:163, 1936.
25. Griggs, D. E., Coggin, C. B., and Evans, N.: Right Ventricular Hypertrophy and Congestive Failure in Chronic Pulmonary Disease, Am. Heart J. **17**:681, 1939.
26. Scott, R. W., and Garvin, C. F.: Cor Pulmonale: Observations in Fifty Autopsy Cases, Am. Heart J. **22**:56, 1941.
27. Goldberger, E.: Unipolar Lead Electrocardiography, Philadelphia, 1947, Lea & Febiger.
28. Myers, G. B., Klein, H. A., and Stofer, B. E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, Am. Heart J. **35**:1, 1948.
29. Myers, G. B., Klein, H. A., Stofer, B. E., and Hiratzka, T.: Normal Variations in Multiple Precordial Leads, Am. Heart J. **34**:785, 1947.
30. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, Am. Heart J. **37**:161, 1949.

Clinical Reports

UNUSUAL FEATURES IN A CASE OF CAROTID SINUS SYNDROME

A. DE VRIES, M.D., AND L. HALPERN, M.D.
JERUSALEM, PALESTINE

SINCE Hering[1] discovered the carotid sinus reflexes and their importance in the nervous regulation of the vascular system, disturbances of the carotid sinus reflexes have become increasingly significant in clinical pathology. The following observation may serve as a contribution to the knowledge of the carotid sinus syndrome.

CASE REPORT

M. D., a 53-year-old man, was readmitted to the hospital for the fifth time in October, 1944, because of attacks of precordial pain, loss of consciousness, and convulsions. At the age of 32 years he fell from a scaffold and fractured the neck of his left femur and several ribs. These injuries were so severe that he was bedridden for two years. He apparently had no intracranial injuries and did not lose consciousness after the fall.

A few months after the accident the patient began to experience attacks of pressure and pain in the precordial region; these usually subsided quickly. During severe attacks, loss of consciousness and convulsions occurred. These symptoms were not present without preceding precordial pain. The frequency of these attacks was quite variable, being absent for periods of one year or recurring many times during one month. Several times during the last few years he was brought to the first aid station of our hospital in an unconscious state.

During the last twelve years the patient suffered, in addition, from attacks of dyspnea accompanied by precordial pain radiating to the left shoulder and arm. At times the patient was persistently dyspneic for periods of days or a week. During these periods severe attacks of asthma, precordial pain, and convulsions were observed. The attacks of precordial pain were independent of excitement, exertion, meals, and cold. The effect of nitroglycerine on the pain and of ephedrine on the dyspnea was inconsistent.

On repeated admissions to the department of internal medicine during the years 1940 to 1944, inclusive, examination revealed the same essential findings. The patient had a plethoric, masklike face and was in good general condition. The pulse was regular at a rate of 80 beats per minute. Between the attacks the blood pressure varied between 125/80 and 155/110. The heart was of normal size and the sounds were of good quality. X-ray films of the heart and electrocardiograms were normal. There were no remarkable findings in the lungs. However, during the periods of dyspnea, expiration was prolonged and dry râles were heard diffusely over both lungs.

From the Department of Internal Medicine, Division B, and the Department of Clinical Neurology, Hadassah Rothschild University Hospital, Jerusalem, Palestine.

Neurological examination revealed the following pathologic findings: slight nystagmus on fixation, especially when looking to the right side, motor hemiparesis, a slight but distinct central hemihypoesthesia on the left side, and slight hypostereognosis with the left hand. Other disturbances in the nervous system were not found. Urine, blood count and smear, and blood chemistry (urea, sugar, and cholesterol) were normal. On repeated examinations during several admissions the blood Wassermann reaction was negative.

During this present admission it was observed that the typical complete attacks could be produced by pressure on the left carotid sinus region. The slightest pressure was sufficient to produce an attack. No disturbance appeared with pressure on the right side. Palpation of the carotid sinus region on the left and right sides showed no abnormal masses. The spontaneous attacks observed during the patient's stay in the ward were entirely similar to those produced by pressure on the left carotid sinus region.

Phenomena Produced by Pressure on the Left Carotid Sinus as Observed During Admission in 1944.—On slight pressure on the left carotid sinus region, almost instantly the patient experienced a feeling of pressure in the cardiac region and clutched the left chest. At the same time his face assumed an anxious expression and turned red while sweat poured from his forehead and temples. He became short of breath, with difficult and prolonged expiration. At this time wheezing was heard. A few seconds later he became unconscious and convulsions appeared on the right side only. The head was turned to the extreme right and the whole body was turned to the same side. The arms were crossed over his breast. The left leg was bent, while the right leg was stretched out. The pupils were dilated and did not react to light. There was no incontinence of urine, nor was the tongue bitten. There was no Babinski sign. During the attack the pulse was regular and attained a rate of 120 to 140 per minute. Blood pressure readings between the convulsions rose from 125/80 to 180/120. The attacks lasted from a few minutes to one-half hour. An attack could be prolonged at will by the slightest touching of the patient or even of his bed. When the attack was subsiding, slight movement of the bed was sufficient to re-excite turning of the head to the extreme right, stretching of the right leg, bending of the left leg, and then convulsions of the whole body. After the attack, consciousness was regained in a few minutes, but the patient remained confused and dumb for a period varying from one to six hours. With the subsidence of the convulsions the pulse rate and the blood pressure returned to normal and the dyspnea and wheezing disappeared gradually. At times, however, when the patient was in a dyspneic phase, wheezing and prolonged expiration continued for many hours.

Five completely identical attacks were elicited by application of pressure to the left carotid sinus region. Pressure on the right carotid sinus region did not produce attacks. Repeated examination of the blood sugar during the attacks revealed essentially normal values and at no time was hypoglycemia or hyperglycemia observed.

Interrogation of the patient revealed that the attacks came on without his being aware of having applied or having experienced pressure to the neck. It is noteworthy, however, that turning of the head to the extreme right by the physician produced in the patient an unpleasant feeling as though an attack

were imminent. It is also noteworthy that the patient preferred to wear a shirt open at the neck.

The patient refused exploration or even novocainization of the carotid sinus region.

COMMENT

This is a case of carotid sinus syndrome, if we accept as its definition a clinical syndrome which can be elicited by pressure on the carotid sinus region. It is well known that in patients suffering from this disturbance, spontaneous attacks may occur without obvious pressure on the carotid sinus region.

Weiss and Baker[2] classified the carotid sinus syndrome into three types: (1) syncope accompanied by slowing of the pulse; (2) syncope accompanied by low blood pressure; and (3) syncope with various neurological features, but unaccompanied by bradycardia and hypotension. The case which has been described apparently belongs in the last category. The patient presented some unusual features from the medical and neurological point of view, rarely observed in the carotid sinus syndrome.

The precordial pain, radiating into the shoulder and arm and accompanied by anxiety, was clearly of the anginal type. It is known that in some patients pressure on the carotid sinus may induce an attack of angina pectoris.[3] There are two considerations supporting the opinion that in our patient no organic disease of the coronary arteries was present. The first is the fact that after seventeen years of repeated attacks of "angina pectoris" no roentgenologic evidence of cardiac enlargement nor any abnormality in the electrocardiograms was found. The second is that neither exertion, cold, meals, nor excitement induced attacks of precordial pain. It is, therefore, improbable that relative myocardial ischemia was induced by the tachycardia, per se, which occurred during the attacks. It has to be assumed that in this case pressure on the carotid sinus led to a spasm of the coronary arteries.

The attacks of dyspnea were clearly caused by bronchiospasm. The clinical picture, the absence of cardiac enlargement, and the finding of a normal arm-to-tongue circulation time during a period of dyspnea are evidence against dyspnea of cardiac origin. Respiratory distress and orthopnea have been observed often in carotid sinus syndrome. Attacks of bronchial asthma, however, seem to be unusual. The bronchial spasm existing in this case is different from the deepened and accelerated respiration usually observed as a result of pressure on the carotid sinus in animals.

Although slight acceleration of the pulse rate during attacks of carotid sinus syndrome sometimes has been observed, tachycardia such as that found in the present case seems to be rare. A rise in blood pressure during the attacks of carotid sinus syndrome is also unusual. Danielopolu and associates[4] distinguished between two types of blood pressure reactions following carotid sinus pressure in man. In most cases they found a reduction of blood pressure; in only a few cases, an increase. It is of interest, in this respect, that, according to Danielopolu,[5] pressure on the carotid sinus in monkeys always results in

an increase of blood pressure. In healthy subjects Tomanek[6] observed a slight increase in blood pressure, up to 10 mm.Hg, following carotid sinus pressure. Weiss and Baker[2] also observed a slight rise in blood pressure after carotid sinus pressure in a few healthy subjects. The highest blood pressure rise found by Mandelstamm and Lifschitz[7] in healthy subjects as a result of carotid sinus pressure was 30 mm. of mercury. The latter authors, like Weiss and associates,[2,8] believe that in most cases the stated increase in blood pressure was due to a faulty technique of application of pressure to the carotid sinus region, namely, obstruction of the common carotid artery below the point of its division, leading to a decrease in pressure in the carotid sinus. In our case pressure on the common carotid artery below the region of the carotid sinus had no effect whatsoever. Another explanation of the occurrence of increased blood pressure and also of dyspnea following pressure on the carotid sinus region is the possible induction of anoxemia of the carotid bodies. Some investigators[9,10] were able to cause severe dyspnea in the dog by obstructing the blood supply to the carotid bodies. The tachycardia observed in our patient, however, seems to invalidate this latter explanation, since in the animal experiment anoxemia of the carotid bodies leads to bradycardia.

In the differential diagnosis a pheochromocytoma has to be considered as accounting for the attacks of tachycardia, hypertension, and sweating. Nuzum and Dalton[11] described a case of suprarenal pheochromocytoma in which pressure on the carotid sinus elicited attacks characterized by precordial pressure, sweating, and hypertension, but only slight increase in pulse rate; these were identical with those occurring spontaneously. In our patient no evidence of suprarenal medullary tumor was suggested by x-ray and blood sugar studies. Although the possibility cannot be excluded, the duration of the disease for seventeen years makes the diagnosis of pheochromocytoma improbable.

The neurological syndrome in our patient, consisting of left hemiparesis, hemihypoesthesia, and hypostereognosis was present on the first examination and did not develop further in the following years. It may be assumed that this syndrome developed as the result of the thrombotic occlusion of a blood vessel, occurring during a "carotid sinus" attack. Marmor and Sapirstein[12] observed in a patient the development of left-sided hemiplegia after pressure on the right carotid sinus. At autopsy bilateral thrombosis of the anterior cerebral arteries was found. Askey,[13] discussing seven cases of transient contralateral hemiplegia occurring after carotid sinus pressure, points out that persistent hemiplegia, developing in the syndrome, is probably due to thromboses or hemorrhages. In our patient, the affected sensibility of the left side points to the involvement of the right artery of the sylvian fissure, the cerebral vascular disturbance, therefore, being localized contralateral to the hypersensitive carotid sinus. The finding of Marmor and Sapirstein[12] of bilateral thrombosis after unilateral carotid sinus pressure makes the assumption of a vascular occlusion contralateral to the hypersensitive carotid sinus in our patient quite possible.

Convulsions are a common feature of the carotid sinus syndrome of the cerebral types. Weiss and Baker[2] reported the occurrence of generalized tono-

clonic convulsions, as well as unilateral jacksonian attacks. The convulsions in our patient, characterized by turning of the head, the eyes, and the whole body to the right, stretching of the right leg, and bending of the left leg, are of a special type and belong to the group of "frontal epilepsy." Foerster[14] provoked in man typical convulsions by electrical irritation of the frontal lobe. These convulsions consisted in a conjugated turning of the head, the eyes, and the body to the contralateral side with subsequent tonoclonic convulsions in the contralateral extremities. The area where the convulsions originate, called by Foerster "frontal adversive area," is situated in the centrofrontal region and corresponds to Field 6 of Brodmann[15] and Area F B of Von Economo and Koscinas,[16] which is the area agranularis frontalis. This area, because of its agranulated structure, is connected with the gigantopyramidal cortical area rather than with the other frontal types, which have an interior granulated layer. On the basis of the observations of Goldstein and associates[17] and Zingerle,[18] as well as the observations of one of us (L.H.),[19,20] it has been pointed out that the "frontal" convulsions observed in man correspond clinically in essence to the experimentally produced attack, although with certain variations. In some cases the chief symptom is a forcibly conjugated turning of the head and the eyes to the contralateral side, while the arm and sometimes the leg of the homolateral side are stretched. Finally, there are cases of frontal epilepsy in which both upper extremities take part, the convulsions then having the features of a partial neck reflex. In our patient the convulsions showed the features of a neck reflex, manifesting themselves in the lower extremities by producing stretching out of the leg on the side to which the chin was turned and bending of the other leg. Our observations thus show that in addition to the generalized attack and the unilateral jacksonian attack, the unilateral attack of "frontal" convulsions also can be produced by irritation of a hypersensitive carotid sinus. In our patient pressure on the left carotid sinus produced a contralateral "frontal attack," possibly caused by a reflex anemia of the hemisphere of the same side. Why in one case a generalized attack occurs and in the other a unilateral jacksonian attack or a "frontal" attack is at present not understood.

SUMMARY

A case of carotid sinus syndrome is reported with the unusual medical features of bronchiospasm, tachycardia, and increase in blood pressure. From the neurological point of view the contralateral attack of convulsions having the main features of a partial neck reflex and belonging to the type of frontal epilepsy are of interest.

REFERENCES

1. Hering, H. E.: Die Karotidsinusreflexe auf Herz und Gefaesze, Dresden and Leipzig, 1927, Theodore Steinkopff.
2. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, Medicine **12**:297, 1933.
3. Friedman, M.: The Anginal Syndrome as a Manifestation of Hyperactivity of the Carotid Sinus, Am. Heart J. **29**:37, 1945.

4. Danielopolu, D., Marcu, I., and Proca, G. G.: Sur la mecanisme de production des variations du reflexe sino-carotidien à l'etat pathologique, Compt. rend. Soc. de biol. **109**:767, 1932.
5. Danielopolu, D., Aslan, A., Marcu, I., Proca, G. G., and Manescu, E.: Les zones reflexogenes carotidiennes, Presse méd. **35**:1585, 1927.
6. Tomanek, Z.: Carotissinusreflexe Beim Menschen, Klin. Wchnschr. **7**:898, 1928.
7. Mandelstamm, M., and Lifschitz, S.: Vegetative Herzreflexe, 4 Mitteilung. Die Wirkung der Karotissinusreflexe auf den Blutdruck Beim Menschen, Wien. Arch. f. inn. Med. **22**:397, 1932.
8. Ferris, E. B., Jr., Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, Medicine **14**:377, 1935.
9. Winder, C. V., Bernthal, T., and Weeks, W. F.: Reflex Hyperpnea and Vasoconstriction Due to Ischemic Excitation of the Carotid Body, Am. J. Physiol. **124**:238, 1938.
10. Schmidt, C. R., and Comroe, J. H.: Functions of the Carotid and Aortic Bodies, Physiol. Rev. **20**:115, 1940.
11. Nuzum, F. R., and Dalton, J. W.: Paroxysmal and Persistent Hypertension in Association With Lesions of Adrenal Glands, Am. Heart J. **16**:643, 1938.
12. Marmor, J., and Sapirstein, M. R.: Bilateral Thrombosis of Anterior Cerebral Artery Following Stimulation of a Hypersensitive Carotid Sinus, J. A. M. A. **117**:1089, 1941.
13. Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation, Am. Heart J. **31**:131, 1946.
14. Foerster, O.: Die pathogenese des Epileptischen Krampfanfalles: Einleitender Ueberblick, Klinik und Therapie, Deutsche Ztschr. f. Nerven. **94**:3, 1926.
15. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf grund des Zellenbaues, Leipzig, 1909, J. A. Barth.
16. Von Economo, C. F., and Koscinas, G. N.: Die Zytoarchitektonik der Hirnrinde des Erwachsenen Menschen, Berlin, 1925, Julius Springer.
17. Goldstein, K., and Boernstein, W.: Ueber sich in Pseudospontanen Bewegungen Aeuszernde Spasmen und ueber Eigentuemliche Stellungen bie "Striaeren" Eerkrankungen. Zugleich ein Beitrag von den Mitbewegungen, den Induzierten Tonusaenderungen und dem Phaenomen der Reflexumkehr, Deutsche Ztschr. f. Nerven. **84**:234, 1925.
18. Zingerle, H.: Automatosesyndrom bein Linksseitiger Stirnhirnekrankung, Ztschr. f. d. ges. Neurol. u. Psychiat. **145**:249, 1933.
19. Halpern, L.: Ueber Frontale Epilepsie, Wien. klin. Wchnschr. **18**:557, 1935.
20. Halpern, L.: Ueber ein Wendungssyndrom des Stirnhirns, Wien. klin. Wchnschr. **15**:505, 1937.

AURICULAR FLUTTER DURING THE ADMINISTRATION OF CYCLOPROPANE AND CURARE

Report of Two Cases

Donald L. Mahanna, M.D., Thomas E. Clark, M.D., and R. W. Kissane, M.D.

Columbus, Ohio

CURARE was first used in anesthesia by Griffith and Johnson,[1,5] and Cullen[3] reported its use in a large number of cases. The alkaloid of curare in use is *d*-tubocurarine, which in therapeutic doses is thought to have no effect upon the electrocardiogram of the normal or diseased heart nor on involuntary or cardiac muscle.[4] On the other hand, cyclopropane is a very common producer of cardiac arrhythmia; therefore, it was thought advisable to report the following two cases.

Case 1.—A. E. was a 74-year-old white man who had a negative family history and past history. He had enjoyed good health except that for a number of years he had had attacks of epigastric discomfort, with frequent urination and nocturia. Ten days before admission to the hospital he had severe abdominal pain, with return of the polyuria. Physical examination showed an arcus senilis with arteriovenous nicking and narrowing of the retinal arteries. The only other positive findings were limited to the abdomen, where there was deep tenderness and muscle guarding in the left upper quadrant. The temperature was 100.6° F.; the pulse, 68 per minute and regular; the respirations, 16; and the blood pressure, 110/84. The blood count revealed 3,740,000 red blood cells and 14,300 white blood cells, with 90 per cent polymorphonuclear leucocytes and 10 per cent lymphocytes. The sedimentation rate was 84 mm. in sixty minutes. The urine had a specific gravity of 1.033, 5.0 mg. of albumin, and no sugar. The blood urea nitrogen was 28 mg. and the prothrombin was 92.5 per cent. The Wassermann test was negative. A cyst was discovered in the upper left quadrant of the abdomen, and pyelograms showed it to be on the superior pole of the left kidney and in communication with this organ. An exploratory laparotomy was done and the mass marsupialized. The preanesthesia medication was Pantapon, grain 1/6, and scopolamine, grain 1/200. The anesthesia was Pentothal Sodium and cyclopropane, with the following charted notes: "Pentothal Sodium, 10:55 A.M.; curare, 2.0 c.c., 11:15; curare, 2.0 c.c., 11:25, pulse irregular; curare, 2.0 c.c., 11:45; curare, 2.0 c.c., 11:55; pulse irregular, rate 140, thought to be auricular fibrillation; and at 12:45 P.M. apnea, intercostal paralysis with only diaphragmatic respirations." The electrocardiogram showed auricular flutter with 2:1, 3:1, and 4:1 block, and return to a sinus rhythm with a negative T_2 and T_3 and diphasic T_4 in five days, after the administration of quinidine sulfate (Fig. 1). The patient made an uneventful recovery.

Case 2.—E. D., a white married woman, 44 years of age, stated that her mother had died of some type of heart disease, and that she had had growing pains as a child, occasional tonsillitis, with a tonsillectomy at the age of 8 years, and a simple goiter at 11 years of age. At the

From the Cardiological Departments of the Ohio State University, College of Medicine, and White Cross Hospital, Columbus, Ohio.

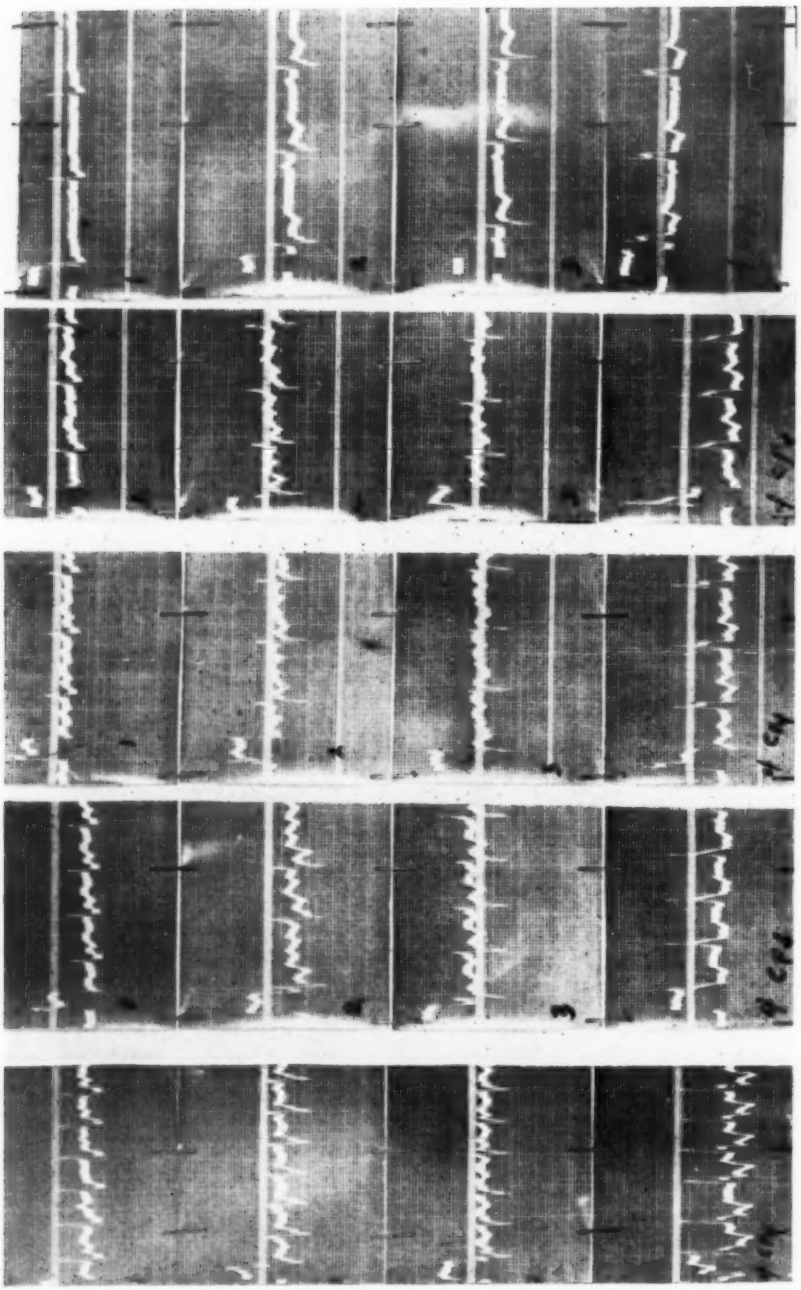


Fig. 1.—Case 1. Electrocardiograms consisting of three limb leads in Lead CF_4 taken on five consecutive days (from left to right). The first four show auricular flutter, and the fifth, sinus rhythm

age of 12, she began to have palpitation, tachycardia, and flushing on exertion. At the age of 31 years, upon considerable exertion, she became quite nervous, had severe tachycardia, palpitation, occasional slight pain in the lower sternal region, slight dyspnea, and an occasional extrasystole.

A physical examination at the age of 31 years revealed the temperature to be 98.6° F.; the respirations, 16; the pulse rate, 104 per minute and rhythm regular; and the blood pressure, 142/74. There was a thrill, presystolic murmur, booming first sound, and mid-diastolic squeaking sound at the apex, with a systolic murmur at the pulmonic area and along the left border of the sternum. The lungs were clear, the liver was at the costal margin, and there was no edema of the ankles. The orthodiagram showed the left auricular shadow enlarged to the left and posteriorly into the posterior mediastinal space. The anterior transverse diameter was 11.7 centimeters. The electrocardiogram revealed a tendency toward a right axis deviation, and there was a rather pronounced P wave in all leads. The basal metabolic rate was plus 11 per cent, and the Wassermann test and urinalysis were negative. The blood count, sedimentation rate, and blood chemistry were normal, and the vital capacity was 100 per cent of normal. The diagnosis was rheumatic heart disease, with mitral stenosis and insufficiency, and hypertrophy and dilatation. The patient was very comfortable and she improved under the routine and accepted treatment, but the subsequent electrocardiograms showed a slightly lowered T wave in Lead II.

One year later she became pregnant and was delivered at term. Ten days following delivery she had a definite increase in the systolic and drop in the diastolic blood pressure, and a diastolic murmur appeared at the aortic area. After two weeks the signs of aortic insufficiency had disappeared; however, the orthodiagram revealed the transverse diameter as 13.5 cm., and since that time it has remained between 12.0 and 12.5 centimeters. The electrocardiograms had remained unchanged. The patient was symptom free until the age of 44 years, when she noticed a tumor mass in her lower abdomen. The blood pressure was 140/80; the cardiac rhythm was regular, with a rate of 80 beats per minute. The vital capacity was 85 per cent. The hemoglobin was 14.1 Gm.; the red blood cells numbered 4,630,000; and the white blood cells, 6,800, with 73 per cent polymorphonuclear leucocytes and 27 per cent lymphocytes. The nonprotein nitrogen was 24.5 mg. per cent; the urine, negative; and the coagulation time, four and one-half minutes. A hysterectomy was performed for the removal of a uterine fibroid. The anesthesia was Pentothal Sodium and cyclopropane, with the following charted notes: "Pentothal Sodium at 10 A.M.; morphine sulfate, grain, 1/6, atropine sulfate, grain, 1/150, at 11 A.M.; cyclopropane and oxygen at noon; curare (Intocostrin) 3.0 c.c. at 12:15 P.M., pulse irregular; rate 110 at 12:20 P.M.; curare 2.0 c.c., pulse irregular, rate 120 at 12:30 P.M.; and at 12:50 P.M. anesthesia was terminated and ephedrine, grain 3/8, was given intravenously." The electrocardiogram showed auricular flutter with 4:1, 3:1, and 2:1 block. The next day the patient was started on 2 cat units of digitalis a day and 15 grains of quinidine sulfate, with an increase of 5 grains a day until the fourth day, when 35 grains of quinidine were given and the auricular flutter disappeared, but the electrocardiogram showed complete heart block. The digitalis and quinidine sulfate were discontinued, and three days later the electrocardiogram showed a normal sinus rhythm with a delay in A-V conduction. However, in one month the tracing was the same as before the operation and anesthesia (Fig. 2).

DISCUSSION

Cardiac irregularities are one of the chief objections to cyclopropane, especially with the higher concentrations of the gas.[6] Cullen[7] stated, "We could demonstrate that curare neither increased susceptibility of the heart nor offered protection to the action of cyclopropane." The experiments upon dogs by Perlstein and Weinglass[8] gave no clear indication as to the exact cause of death in prolonged curarization, but pointed to the heart as the organ principally affected because irregularity or bradycardia was found regularly and the autopsies showed

dilation of the heart. The type of irregularity or bradycardia was not identified and therefore cannot be exactly compared with the disturbance in the two cases reported here: in both cases an irregularity due to auricular flutter, and, in the second case, bradycardia due to complete heart block. These patients received 8.0 and 5.0 c.c. of curare, respectively, which is smaller by comparison than the amounts used in the dog experiments; however, the irregularities occurred immediately after the intravenous injection of only 4.0 and 3.0 c.c. of the drug. Although neither of these patients had a normal heart, one having arteriosclerotic and the other having rheumatic heart disease, they had never had any previous

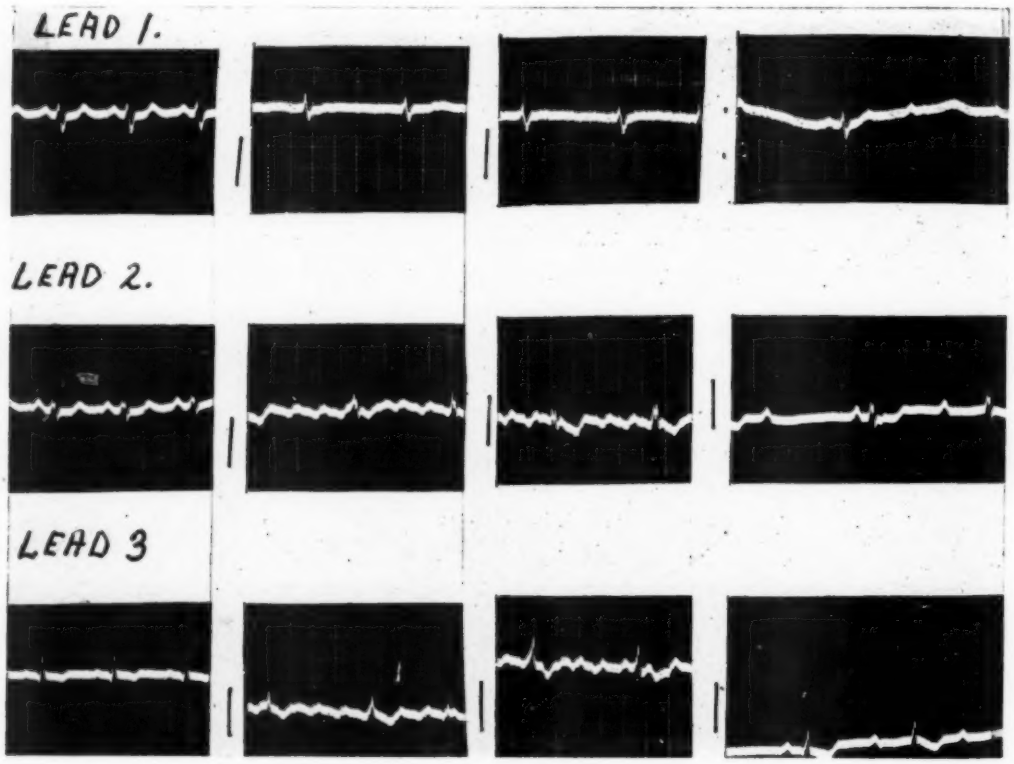


Fig. 2.—Case 2. Electrocardiograms from left to right: a tracing made before curare was given; a tracing taken shortly after injection of curare, showing auricular flutter; a tracing taken one day after injection of curare, showing auricular flutter; a tracing made on the fifth day showing complete heart block. An electrocardiogram made one month later (not illustrated) showed a sinus rhythm with delayed A-V conduction.

irregularity. There did not appear to be any additional heart muscle damage caused by the cyclopropane or curare, because in both cases, when the heart returned to normal sinus rhythm, the electrocardiogram was the same as before the anesthesia. This suggests that the drugs interfered with the normal function of the pacemaker and intrinsic conduction mechanism. Following their experiments, Perlstein and Weinglass concluded that "atropine hastens the lethal effect

of curare," and showed that rapid death occurred in atropinized dogs after curarization, and immediate death, in two dogs, after the injection of a physiologic dose of atropine. The two cases herein reported gave no information relative to the action of atropine and curare because the first received scopolamine, grain 1/200, and the second received atropine, grain 1/150.

CONCLUSION

Two cases of auricular flutter following the use of curare during cyclopropane anesthesia are reported.

REFERENCES

1. Griffith, H. R., and Johnson, G. E.: Use of Curare in General Anesthesia, Anesthesiology **3**:418, 1942.
2. Baird, J. W., and Adams, R. C.: Curare in General Surgery, Proc. Staff Meet., Mayo Clin. **19**:200, 1944.
3. Cullen, S. C.: Use of Curare for Improvement of Abdominal Muscle Relaxation During Inhalation Anesthesia, Surgery **14**:261, 1943.
4. Ruskin, A., Ewalt, J., and Decherd, G.: Electrocardiogram of Curarized Human Patients, Dis. Nerv. System **4**:335, 1943.
5. Griffith, H. R.: The Use of Curare in Anesthesia and Other Clinical Purposes, Canad. M. A. J. **50**:144, 1944.
6. Knight, R. T., and Baird, J. W.: Anesthesia for the Ageing and Aged, Lancet **64**:183, 1944.
7. Cullen, S. C.: Clinical and Laboratory Observations on the Use of Curare During Inhalation Anesthesia, Anesthesiology **5**:166, 1944.
8. Perlstein, M. A., and Weinglass, A.: Fatal Effects of Prolonged Complete Curarization. Am. J. Dis. Child. **67**:360, 1944.

Abstracts and Reviews

Selected Abstracts

Myers, J. D., and Hickam, J. B.: An Estimation of the Hepatic Blood Flow and Splanchnic Oxygen Consumption in Heart Failure. J. Clin. Investigation **27**:620 (Sept.), 1948.

Thirteen patients with congestive heart failure, associated with a reduced cardiac output and increased blood volume, were studied by the hepatic vein catheterization technique. Liver blood flow was determined by the bromsulphalein method.

In cardiac failure the liver gets its usual percentage (20 to 24 per cent) of the reduced total cardiac output, and thus differs from the kidney, which suffers a disproportionate reduction in blood flow. There is a compensatory increase in hepatic artiovenous oxygen difference, which under rest and fasting conditions maintains a normal splanchnic oxygen difference. There is a poor correlation between the level of hepatic blood flow and right atrial or peripheral venous pressure.

WAIFE.

Nelson, H. G., and the Personnel of United States Naval Medical Research Unit 4: Studies on Rheumatic Fever: Observations on Tonsillar Carriers of Hemolytic Streptococci; The Effect of Tonsillectomy and the Administration of Penicillin on Rheumatic and Nonrheumatic Fever Patients. J. Infect. Dis. **83**:138 (Sept.-Oct.), 1948.

A study was made of the comparative incidence of Group A hemolytic streptococci obtained from cultures of the throats and excised tonsils of rheumatic and nonrheumatic fever patients who had been selected for tonsillectomy. Of the seventy-five rheumatic fever patients, twenty-two were considered to have a low-grade activity of the disease and fifty-three showed no evidence of activity for at least one month prior to operation. There were sixty-four nonrheumatic patients.

Routine throat cultures prior to operation were positive for Group A hemolytic streptococci in only 2.7 per cent of the rheumatic fever patients. Positive throat cultures for Group A hemolytic streptococci were similarly found in 3.1 per cent of the nonrheumatic patients prior to tonsillectomy. Group A streptococci were found in the excised tonsillar tissue of 33.3 per cent of the rheumatic fever patients. There was no significant difference in the percentage of positive cultures recovered from patients with continuing activity, as compared with those in the inactive group. Positive cultures were obtained from the tonsils of 15.6 per cent of the nonrheumatic fever patients.

Penicillin was given preoperatively to patients whose cultures yielded hemolytic streptococci. Postoperative penicillin therapy was given to all patients. The twenty-two patients with low-grade activity showed no increase in activity following tonsillectomy, and all but two of this group became inactive within three months. Of the group of fifty-three patients who had been considered inactive at the time of tonsillectomy, ten had minor manifestations of activity following operation, but all became inactive at the end of two months.

The authors conclude that low-grade activity of rheumatic fever does not contraindicate tonsillectomy when combined with postoperative penicillin therapy, and that cultures from excised tonsils appear to give more accurate information as to the actual incidence of streptococcal carriers than do routine throat cultures.

SCHWARTZ.

Gold, H., Modell, W., Kwit, N. J., Shane, S. J., Dayrit, C., Kramer, M. L., Zahm, W., and Otto, H. L.: Comparison of Ouabain With Strophanthidin-3-Acetate by Intravenous Injection in Man. J. Pharmacol. & Exper. Therap. **94**:39 (Sept.), 1948

One milligram of strophanthidin-3-acetate (one of the synthetic esters of strophanthidin) and 0.5 mg. ouabain were diluted to 10 c.c. and administered intravenously to patients with auricular fibrillation and clinical evidence of congestive heart failure. Each patient was given both drugs at different times so that individual variations in response could be controlled. None of the eight patients studied had received any digitalis compounds for at least three weeks prior to the test. Slowing of the ventricular rate was used as an objective sign of digitalization.

Both drugs showed rapid effects. With strophanthidin-3-acetate, 70 per cent of the maximum ventricular slowing was seen within five minutes and the maximum slowing occurred within ten minutes. The ventricular rate returned to its preinjection level in four hours or less. With ouabain, 50 per cent of the maximum slowing was evident within ten minutes and the maximum effect occurred within one to two hours. The ventricular rate did not return to its preinjection level for thirty-six hours. No toxic effects were noted with either drug. There was improvement in the clinical picture coincident with the slowing of the ventricular rate.

The transitory, extremely rapid, and moderately short duration of action of strophanthidin -3-acetate suggests that it might be of therapeutic value in acute cardiac emergencies, such as paroxysmal pulmonary edema, and in some of the paroxysmal tachycardias. Its relatively short duration of action would decrease the danger of prolonged toxic reactions in patients receiving digitalis compounds.

GODFREY.

Donovan, G. E.: Modern Phonocardiography. Lancet **6524**:401 (Sept. 11), 1948.

The modern practice is to record the heart sounds linearly, stethoscopically, or logarithmically. The author describes a phonoelectrocardioscope which permits the direct, instantaneous, simultaneous, and constant viewing of a pair of cardiac phenomena such as the phonocardiogram and electrocardiogram. The phonocardiogram represents amplified heart sounds recorded logarithmically. The instrument consists of a double-channel electronic valve amplifying unit with frequency control, intensity control, tone-compensated volume control, a double-beam cathode ray oscilloscope, and a long-persistent fluorescent screen. If permanent records are desired, photographs can be taken of one traverse of the cathode-ray spots on the screen. Several still photographs of the fluorescent screen are demonstrated as examples.

The author suggests that many of the inaudible vibrations which can be recorded (such as the four components to the first and second heart sounds) may eventually prove to have almost as much clinical significance as have the cardiac sounds and murmurs.

WAGNER.

Wolff, G.: Childhood Mortality From Rheumatic Fever and Heart Diseases. Child. Bureau Pub. 322, Washington, D. C., 1948.

In a statistical study of death rates in the United States during the years 1939 to 1941, it was found that at least 12,000 deaths were caused by acute rheumatic fever and its sequelae in childhood. Among the nonwhite children with ages ranging from 5 to 19 years, there were 16.6 deaths reported per 100,000 population; among white children the death rate was 11.1 per 100,000. With increasing age in both sexes and racial groups, there was a distinct increase in the death rate for rheumatic heart disease.

The nonwhite group consistently had a higher mortality rate than the white group. This suggests that adverse social and economic conditions are important factors. When analyzed by geographic divisions, these race differences were most significant in the Middle Atlantic States, but in the Mountain State division, higher death rates were observed for white children, as compared with nonwhite children.

No consistent sex differences in mortality rates were seen, except in the group between the ages of 15 to 19 years. In this age group the nonwhite females showed a distinctly higher rate than nonwhite males, while in the white group the rate for females was lower than for males.

In general, the mortality rate is highest in the Middle Atlantic States and lowest in the Pacific Coast States. In the Mountain Division, the rate was exceptionally high for the white children in all age groups.

The range of the crude rate for mortality from acute rheumatic fever plus diseases of the heart ranged from 5.3 in Vermont to 22.4 in Utah; the average for the United States was 11.7 per 100,000.

WAIFE.

Luisada, A., and Fleischner, F. G.: Studies of Fluorocardiography: Tracings of the Left Ventricle in Myocardial Infarction. Acta cardiol. 308 (No. 4), 1948.

Twenty patients with old or recent myocardial infarctions were studied by means of fluorocardiography. The graphic study was made in the posteroanterior position and in both anterior oblique positions.

Several abnormalies of ventricular systole and diastole were recognized. Among these, lack of pulsation and inverted pulsation (paradoxical pulsation) in a circumscribed area were considered as the most significant findings, the former, pointing to an area of "local paralysis"; the latter, to a "dynamic aneurysm" of the ventricular wall. Evaluations of the dynamic results of such abnormalities are given. The reasons for suggesting the two new terms are discussed.

Correlation of the findings with electrocardiographic data revealed a coincidence of about 90 per cent. In general, the area presenting an abnormality of contraction was found to be more extensive than indicated by the electrocardiogram.

The findings confirm those of previous roentgenkymographic studies. The reasons for a greater exactitude and broader applicability of fluorocardiography in comparison with roentgenkymography are given.

AUTHORS.

Bechgaard, P.: Paroxysmal Ventricular Fibrillation With Recovery. Acta med. Scandinav. **132**:9 (No. 1), 1948.

Twenty-five cases with electrocardiograms showing transient ventricular fibrillation are cited from the literature. All of the patients had severe heart disease, usually with A-V dissociation. All but three died shortly after the fibrillation was recorded. Two patients were able to return to work and the author adds the report of a third instance.

A 50-year-old man with a history of rheumatic fever at the age of 28 had fainting fits for several years, then a six-months' remission, following which he developed nocturnal palpitation and spells of dyspnea with a decreased diurnal exercise tolerance. He then had several fits consisting of sudden disappearance of the pulse, cyanosis, focal convulsions, and hyperpnea, with the return of an irregular pulse which then became regular. An electrocardiogram was normal five days before the attacks, with a P-Q interval of 0.20 second. During two attacks, however, ventricular fibrillation was recorded and in a third the entire electrocardiograph sequence of (1) ventricular flutter-fibrillation for 125 seconds, (2) asystole for 1.4 seconds, (3) A-V dissociation with variable ventricular complexes and an auricular rate of 100 per minute, (4) a prolonged P-Q interval, and (5) a normal tracing six minutes after the attack.

Strophanthus, 0.25 mg., was given twice at four-hour intervals with cessation of the attacks during one night. Three attacks occurred the next morning but with another 0.50 mg. of strophanthus, together with digitalis for more prolonged action, no more attacks occurred. There were no evidences of a cardiac lesion aside from the arrhythmia. The patient was able to return to work and an electrocardiogram was normal six months after discharge. He had only one questionable attack in the thirteen months following hospitalization but dropped dead at the end of this period.

Necropsy showed slight, nonstenosing coronary atheroma and a heart which weighed 330 grams, but no other abnormalities, gross or microscopic. The cause of the disturbance of rhythm was therefore unknown.

SAYEN.

Eckerstrom, A.: Libman-Sacks Syndrome. Acta med. Scandinav. **132**:21 (No. 1), 1948.

The author presents the case history of a 45-year-old woman who had had bone tuberculosis and Graves' disease with a thyroidectomy in the past but who was in good health for five years preceding the development of joint pains and stiffness followed by fever, acrocyanosis, digital pea-sized spots of purple color, butterfly cyanosis of the face, and retinal perivascular lesions. Studies revealed anemia and hyperglobulinemia. The sedimentation rate was 120 mm. per hour at room temperature and 31 mm. per hour in a refrigerator. The increased protein was mainly a gamma globulin which migrated on electrophoresis somewhat more rapidly than the normal gamma fraction does. The albumin-globulin ratio became 1:2. Death occurred after eight months, having been preceded by increased erythema of the cutaneous lesion, higher fever, and signs of polyserositis. At autopsy there was a pericardial effusion, a small amount of ascites, a swollen, fatty liver, and slight splenomegaly. Histologic study revealed increased myocardial, splenic, and lymphatic connective tissue, with vascular fibrinoid changes especially in the precapillaries. The glomeruli were swollen and infiltrated with cells. No endocarditis was present and the heart valves were not described. The clinical and microscopic picture is considered to be that of Libman-Sacks disease. The importance of suspecting such a condition in the presence of hyperglobulinemia, fever, arthritis, and polyserositis is stressed.

SAÄYEN.

Lazarus, S., Munro, H. N., and Bell, G. H.: Capillary Strength Tests in Scurvy and Their Reactions to Vitamin C and Vitamin P Therapy. Clin. Sc. **7**:175 (No. 2), 1948.

These authors used the positive pressure tests of Göthlin and the negative pressure tests of Scarborough in three groups of patients who were studied for capillary fragility. One comprised fifteen patients with scurvy (mean age, 62 years). Subcutaneous hemorrhages and petechiae were found in all of this group. Plasma levels of ascorbic acid and ascorbic acid saturation tests were compatible with the diagnosis of scurvy. The second group comprised twenty-nine male patients (mean age, 74) who served as in-patient controls. The third group consisted of twenty healthy hospital visitors of approximately the same age. The patients with scurvy were placed on a diet free of vitamin C and vitamin P and measurements of capillary strength were made before treatment and at weekly intervals thereafter.

Although the mean number of petechiae obtained by the positive pressure test was greater in the scorbutic than in the nonscorbutic patients, the overlap was so great that it was not considered of diagnostic value. After large doses of ascorbic acid (an average of 9.6 Gm. over a twenty-day period), the signs and symptoms of scurvy cleared up completely in every case; but in the group as a whole the mean petechial readings obtained with both positive and negative pressure tests were unchanged by the administration of ascorbic acid.

Several preparations said to have vitamin P activity were given to scorbutic patients with and without previous treatment with ascorbic acid. No alteration in the capillary strength as measured by the positive pressure test was noted. There was a slight increase in the capillary strength in one skin area as judged by the negative pressure test.

It would appear that the poor correlation between the positive and negative pressure test in individual cases can be explained only in that they measure quite different properties. The authors conclude that these tests of capillary strength do not measure the fundamental vascular lesion in scurvy. They suggest that scurvy is more likely to develop in subjects who already have some form of capillary weakness, that is, that individuals with weak capillaries develop scurvy after a smaller deficiency of vitamin C than do those with strong capillaries.

WAIFE.

Berg, W., Delius, L., and Schildge, E.: Hypnosis and Venous Pressure. Ztschr. f. Kreislaufforsch. **37**:691, 1948.

Induced emotional upsets and suggested exercises during hypnosis resulted in an appreciable rise of venous pressures in six subjects. This was largely independent of arterial pressures, respiration, muscular contraction, and intramuscular pressures.

HECHT

Ashworth, C. T., and Haynes, D. M.: Lesions in Elastic Arteries Associated With Hypertension. Am. J. Path. **24**:195 (Jan.), 1948.

The authors describe a lesion different from the commonly known types of arterial disease in the elastic arteries in three hypertensive patients. The description of this lesion is apparently new. In one of the three patients there was thrombosis of the aorta and other arteries, and in another patient there was thrombosis of the left common carotid artery. All three patients showed a definite histologic finding, namely, a pathologic process in the medial coat involving chiefly the outer musculoelastic layers, which were partially collapsed. Some elastic fibers were broken into small refractile particles. This outer portion of the medial coat, atrophic and collapsed, was the site of marked cellular infiltration, due in part to fibroblasts and to new capillary formation and in part to moderate numbers of lymphocytes scattered diffusely throughout this area, more numerous around capillaries and areas of fibrotic proliferation. In one patient there were, in addition, small foci of coagulative necrosis in the outermost portion of the media, and in such areas polymorphonuclear cells predominated. In the adventitia there was a slight to moderate infiltration of lymphocytes, primarily collected in the region of blood vessels, but not forming perivascular collars characteristic of syphilis. This inflammatory process did not involve the vasa vasorum, and these vessels were not the seat of endarteritis. In the zone of contact between the adventitia and the outer layer of the media there was increased fibrosis leading to scar formations. Collagen bundles in the adventitia near the media were markedly fragmented, and showed in some places early coagulative or fibrinoid necrosis. While the vasa vasorum did not show endarteritis, their medial walls were definitely hypertrophied. Atherosclerosis of the aortic intima in all three patients was slight to moderate; in the third patient it was advanced, but not in the areas where the pathology was noted.

Using this small group of three cases as the basis of their report, the authors examined a group of forty patients with hypertension. Atherosclerosis was present to some degree in every case. In fifteen of these patients atherosclerosis of the elastic arteries was the only alteration present on gross examination. Twenty-three patients showed some degree of histologic alteration of the aorta which the authors think is distinct from the effects of atherosclerosis. The thoracic aorta and the large elastic arteries that leave the aortic arch showed changes similar to those which are described, namely, atrophy and collapse in the outer portion of the media, areas of fibrous replacement and mucoid degeneration, and cellular infiltration by lymphocytes and polymorphonuclear leucocytes around blood vessels, but without distinct collar formation around the vasa vasorum. The latter, however, all showed hypertrophy of their medial coat.

In a control group of fifty patients without hypertension, the microscopic examination did not show alterations approaching those just described, despite the presence of marked atherosclerosis in many of them.

In the hypertensive series the authors could find no correlation between the incidence or the severity of the changes in the aorta, and the age or sex of the patients, the presence of uremia, the level of the blood pressure, the etiological factors of the hypertension, or the presence of syphilis. The absence of eosinophils in the lesions, the principal involvement of the media, and the hypertrophy of the media of the vasa vasorum all constituted distinct differences between these lesions and those of periarteritis nodosa. None of the three patients reported had received sulfonamide drugs, and it is certain that syphilis played no role in the pathology. Erdheim's medionecrosis involves a central portion of the media and is a cystic necrosis, devoid of cellular reaction such as was noted in this study.

The authors believe that this lesion is the result of a vasoconstrictive anoxia involving especially the vasa vasorum, and that multiple minute thrombosis is the underlying cause for the recorded changes.

GOULEY.

Simkin, B., Bergman, H. C., Silver, H., and Prinzmetal, M.: Renal Arteriovenous Anastomoses in Rabbits, Dogs and Human Subjects. Arch. Int. Med. **81**:115 (Feb.), 1948.

The authors injected a mixture consisting of 2.0 Gm. of glass spheres, suspended in 100 c.c. of a gelatin-radiopaque mass warmed to a temperature of 40° which had been perfused through it.

The mass was injected at a pressure from 50 to 100 mm. of mercury. The radiopaque mass issued from the renal vein and was collected in a test tube; in every instance, glass beads were recovered from this perfusate.

This mixture was injected into sixteen isolated human kidneys with intact capsules. Beads 90 to 440 microns in diameter were recovered from the renal vein in ten of the sixteen kidneys; the maximum diameters were 200 microns or more. Neither age nor disease played a role in determining the size of the beads recovered. The same results were obtained when decapsulated kidneys were used.

The authors conclude that these observations indicate the presence of direct arteriovenous communications which must by-pass the capillary bed in the normal human kidney since these spheres were too large to pass through the capillaries.

This experiment was repeated in living rabbits and dogs under ether anesthesia, using a saline suspension of beads and using the lungs as the trap for the beads instead of cannulizing the renal vein. Beads ranging in size from 50 to 180 microns were recovered from the lungs of the rabbits. In seven animals the kidneys were intact and in seven the kidneys were decapsulated. The results indicate the presence of arteriovenous shunts in the kidneys of living rabbits and dogs.

The authors finally conclude that if the concept of a functional extraglomerular circulation in the normal kidney is accepted, based upon their experiments, a re-evaluation of the dynamics of renal flow of the blood is in order.

BERNSTEIN.

Kallner, S.: Thrombosis as a Complication of Internal Diseases. Arch. Int. Med. **81**:126 (Feb.), 1948.

The author studied patients with pneumonia in whom fever persisted after the pneumonia had been apparently controlled by antibiotic therapy. The author used heparin and Dicumarol to treat the thrombosis, which he feels causes the fever to persist and which he thinks is located in the venous system either of the pelvis or of the lower extremities. With this therapy he gives massage to the lower extremities and permits early movement of the lower extremities and trunk. Therapy is continued until the patient is out of bed and moving about freely. The same technique is used for suspected thrombotic complications in the treatment of cases of heart disease, anemia, parturition, and elderly patients who have been confined to bed for a long time for any reason and in any cases in which a manifest thrombosis has been present.

He states that though he has used anticoagulants in the treatment of cardiac infarctions, it is too early to make any statements regarding the results. Heparin was also used in a case of transfusion reaction in which there was anuria. Two hours after the start of heparin therapy the anuria cleared up and long fibrin casts of tubuli were voided.

Finally, in fibrinous bronchitis heparin was used to decrease or counteract the deposit of fibrin, and, when combined with ephedrine and epinephrine, is characterized by the author as "life saving."

BERNSTEIN.

Thomas, S. F., Alto, P., and Garland, L. H.: Roentgen Cardiac Kymography: Electrocardiographic Correlation. California Med. **68**:126 (March), 1948.

The purpose of this paper is to re-evaluate the roentgen cardiac kymograph and to demonstrate that the kymogram sometimes gives information which is not obtainable by any other means.

Routinely, exposures of 1.5 to 2 seconds were made in mid-inspiration with the patient as relaxed as possible in order to avoid a Valsalva or Müller effect. Films in forced inspiration and expiration were made on occasion to confirm or rule out certain minimal findings. The criteria for kymographic diagnosis were the depth (or height), shape, and phase of the waves. The authors found that in most of the patients in this series the waves were usually under 4 mm. in depth. However, in the patients with myocardial disease of any type, the height (or depth) of the waves was often 2 mm. and frequently less than 1 millimeter. Other findings sometimes suggestive of disease of the myocardium were "peaking" of the waves where the waves come to an abrupt point. Splintering of the waves (both systolic and diastolic) was regarded as important

in the diagnosis of disease, especially when it was accompanied by waves of low amplitude which appeared fuzzy (unsharp). The suppression of waves or absence of movement, or the outright reversal of movement, in any area was considered diagnostic of myocardial damage, and when this occurred in the presence of suitable associated findings, an area of infarction was diagnosed. Localized adhesive pericarditis may produce suppressed and fuzzy waves and mimic an area of localized myocardial damage, but the condition was not encountered in this series. The term myocardial damage is used in this report to include various cardiac abnormalities from myocarditis through myofibrosis to frank infarction.

Over 350 sets of kymograms were made. The authors used the electrocardiogram as an accepted test for the diagnosis of major cardiac disease and then matched the kymogram against this method. The two methods correlated in 80.5 per cent of the cases, or 201 patients. Properly interpreted, roentgen kymograms have been demonstrated as a reliable source of additional information and in a small percentage of cases can provide information not obtainable clinically or even by electrocardiogram.

Illustrative cases are used to bring out the various points of interest.

BELLET.

Rodriguez, R., and Root, H. F.: Capillary Fragility and Diabetic Retinitis. New England J. Med. **238**:391 (March 18), 1948.

This report is concerned with the results of the Göthlin positive-pressure test for determining the capillary fragility in diabetic patients. The findings reported deal with three groups of patients: nonselected diabetic patients; diabetic patients with varying degrees of retinopathy; and patients with diabetic retinitis or retinitis proliferans and high degrees of capillary fragility, who were treated with rutin.

The capillary fragility was found to be increased in forty patients (40 per cent), borderline in four (four per cent), and normal in the remaining fifty-six (56 per cent). Diabetic retinitis and hypertension were the most closely related abnormalities among the forty patients with increased capillary fragility. Twelve of these forty patients with increased petechial counts had retinitis with hypertension and fourteen had retinitis with normal blood pressure. In the group of eight patients with retinitis proliferans the blood pressure was normal in two and above 150/90 in the remaining six. In the entire group, the incidence of poor capillary resistance with hypertension was 27.5 per cent. Among the forty patients with abnormal capillary fragility, normal blood pressure and normal fundi were found in three (7.5 per cent). This group confirms the judgment that increased capillary fragility may be present in young persons with diabetes of long duration as one of the earliest signs of arteriosclerosis, which will subsequently be manifest in nephritis, hypertension, and general arteriosclerosis. Among the fifty-six diabetic patients of the nonselected group who had normal capillary fragility, the fundi were normal in fifty-four and retinal damage was present in only two. From the authors' observations it seems clear that diabetic retinopathy seldom occurs in patients who do not have some degree of increased fragility of the capillary walls.

The authors studied an additional group of fifty-six patients with diabetic retinopathy. The petechial index was increased in forty-seven (83.9 per cent) and borderline in nine (16.1 per cent); no patient was found to be normal.

BELLET.

Bronstein, J.: The P Wave in Precordial Leads in Chronic Bronchopulmonary Disease. Rev. argent. de cardiol. **15**:105 (March), 1948.

No significant abnormalities in the P wave of precordial leads in fifty patients with bronchopulmonary disease of varying severity were noted in a large number of precordial leads taken from the vicinity of the sternum and to the right and left of it. In thirty-five of these subjects a definite P pumonale was present in standard bipolar limb leads.

HECHT.

Etala, F., and Berreta, J. A.: A Clinical and Anatomical Study of the Post-tachycardia Syndrome. Rev. argent. de cardiol. **15**:133 (March), 1948.

A 20-year-old patient had suffered from repeated attacks of paroxysmal dyspnea and was admitted to the hospital during an attack of tachycardia of ventricular origin which had resulted in congestive failure. Following the administration of 4.0 Gm. of quinidine intravenously over a four-day period the normal sinus rhythm was re-established, but the patient exhibited severe toxic reactions including convulsive seizures. The patient recovered. Two years later a similar episode occurred which was controlled by 1.0 Gm. of quinidine given intravenously, but the patient died shortly thereafter in profound shock. Serial electrocardiograms obtained during the first episode revealed sharp inversion of the terminal portion of the T wave in Lead I similar to that observed in anterior myocardial infarction. It reverted to a normal pattern before discharge. On the second occasion inversion of the T wave occurred in all three standard limb leads and in Leads V_4, V_5, and V_6. Although profound myocardial depression may be considered to have been the cause of death, no abnormal pathologic findings were demonstrated at autopsy.

HECHT.

Friedman, S. M., Friedman, C. L., and Polley, J. R.: Potentiation of the Hypertensive Effects of Desoxycorticosterone Acetate (DCA) by Various Sodium Salts. Am. J. Physiol. **153**:226 (May), 1948.

A hypertensive syndrome was produced in rats by the administration of DCA ("hormonal" hypertension). The blood pressure raising effect of the DCA was intensified when organic and inorganic sodium salts were added to the drinking water of the animal, and this seemed to be dependent on the excess intake of the sodium ion. The phosphate ions were found to be damaging to the kidney even in the absence of DCA.

The degree of blood pressure elevation did not parallel the degree of renal damage, but the electrolyte disturbances (depression of potassium and chlorides) seemed to follow impairment of renal function.

Elevation of blood pressure consistently preceded impairment of renal function, but renal hypertrophy was always present when renal function was unimpaired following DCA administration. The authors assume, therefore, that DCA causes an initial intrarenal derangement which may be the cause for the resultant hypertensive syndrome.

HECHT.

Hamilton, W. F., and Remington, J. W.: Some Factors in the Regulation of the Stroke Volume. Am. J. Physiol. **153**:287 (May), 1948.

The authors calculated the stroke volume of the heart from the pressure pulse contour of intact dogs. They recognize three mechanisms which regulate stroke volume.

1. *Change in Peripheral Resistance.*—Acute increases of aortic pressure decrease stroke volume and external cardiac work. Decrease of aortic pressure increases these values. The changes represent mechanical effects in the face of unchanged contractile powers of the heart.

2. *Change in Diastolic Size.*—When induced by acute increases in peripheral resistance, changes in the diastolic size of the heart occur which tend to increase stroke volume. These are rarely sufficient to balance or to overcome the effects listed under (1) even when the pericardium is removed.

3. *Sympathetic and Sympathomimetic Stimulation of Cardiac Muscle.*—If peripheral resistance is not greatly altered, sympathetic stimulation increases the contratile power of the heart and raises stroke volume and external cardiac work.

In these experiments changes in resistance to ejection and myocardial stimulation are more important in regulating stroke volume than changes in diastolic filling pressures.

HECHT.

Hamilton, W. F., Riley, R. L., Attyah, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Noble, R. P., Remington, J. W., Richards, D. W., Jr., Wheeler, N. C., and Witham, A. C.: Comparison of the Fick and Dye Injection Methods of Measuring the Cardiac Output in Man. Am. J. Physiol. **153**:309 (May), 1948.

Two sets of data are being reported: both employ almost simultaneously the dye injection method for estimating cardiac output and the catheterization procedure. In eighteen patients studied in Georgia, oxygen consumption for the Fick formula was obtained through a basal metabolism machine and sampling of the dyed arterial sample was accomplished by a rotating kymograph drum. Mixed blood was obtained from the auricles or ventricles. In the thirty patients studied in New York, samples were obtained from the pulmonary artery or right ventricular outflow tract and dyed arterial samples by means of an escapement mechanism drum. The dyed samples were read with a Beckman spectrophotometer at 625 and corrected for turbidity and hemolysis by readings at 725 and 540, respectively.

In forty-eight determinations on thirty-one subjects the results agreed within 25 per cent in all but six subjects. Scatter was equal so that the means of all determinations were almost identical.

HECHT.

Moore, J. C., Schadle, O. W., and Lawson, H. C.: Measurement of the Circulating Red Cell Volume With Methemoglobin-Tagged Cells. Am. J. Physiol. **153**:322 (May), 1948.

After a suspension of red blood cells containing large amounts of methemoglobin was injected into splenectomized, anesthetized dogs, the circulating red cell volume was calculated from the methemoglobin content of the arterial blood. The values obtained by this method corresponded well with the data obtained from the increase in the volume of packed red cells resulting from the injection of the cell suspension, and the decrease in the hematocrit readings resulting from plasma infusions. The use of methemoglobin-tagged cells produced values consistently lower than those obtained from the usual dye-injection (T-1824) method of determining plasma volume.

Repeated measurements with the methemoglobin method following an increase in the red cell mass produced by the injection of cells or a decrease in cells following hemorrhage gave results which were in close agreement with expected values.

HECHT.

Shipley, R. E., and Helmer, O. M.: Observations on the "Sustained Pressor Principle" in Different Animal Species. Am. J. Physiol. **153**:341 (May), 1948.

Further studies have been made on the sustained pressor principle (SP), a pressor substance found in the plasma of cats during prolonged hypotension. SP is apparently produced by the kidneys during the hypotensive phase. Unlike other pressor agents, SP causes a sustained elevation of blood pressure for several hours when it is injected intravenously into recently nephrectomized cats. In these studies SP could be demonstrated in the plasma of rats and dogs subjected to hypotension by bleeding, and in whole blood obtained post mortem from patients dying after a prolonged period of hypotension.

Nephrectomized dogs, cats, and rats were found to react with sustained pressure elevations to the injections of plasma containing the SP.

After the intravenous injection of semicrude kidney extracts from various species (the horse, sheep, hog, cat, dog, rat, and rabbit) into nephrectomized cats, dogs, and rats and into non-nephrectomized chickens, the plasma of the recipient animals acquired the ability to cause sustained elevation of blood pressure in nephrectomized cats, dogs, and rats, but not in non-nephrectomized chickens. A similar pressor effect active in cats and dogs was noted following the injection of human kidney extracts. The injection of chicken kidney extracts into chickens and cats failed to produce any SP in their plasma.

The sustained elevation of pressure following the injection of active plasma appears to be caused by continuous circulation of a rather stabile pressor principle.

HECHT.

Folk, B. P., Zierler, K. L., and Lilienthal, J. L., Jr.: Distribution of Potassium and Sodium Between Serum and Certain Extracellular Fluids in Man. Am. J. Physiol. **153**:381 (May), 1948.

The distribution of potassium and sodium between the serum and extracellular fluids was examined by flame photometer analyses. The mean distribution ratio of the potassium was only slightly lower than that for the sodium:

$$\text{mean } \frac{\text{K fluid}}{\text{K serum}} = 0.92; \quad \text{mean } \frac{\text{Na fluid}}{\text{Na serum}} = 0.96.$$

This discrepancy seems to be due to a loss of potassium from the cells to the serum during the process of obtaining and preparing the blood sample. The potassium distribution ratio here obtained is unexpectedly high, and since it approaches that of the sodium, it appears that part of the potassium is freely diffusible and is distributed across membranes according to the Gibbs-Donnan equilibrium in a manner similar to the sodium, chloride, and bicarbonate ions.

HECHT.

Ferraro, L. R., and Angle, R. G.: Pheochromocytoma With Symptoms of Epinephrine Shock. Arch. Int. Med. **81**:793 (June), 1948.

A case of pheochromocytoma occurring in a 32-year-old soldier which did not present the classic symptoms usually associated with the disease, and which terminated fatally after "epinephrine shock," is reported. It appears that the syndrome during an "epinephrine crisis" results from an abnormal release of epinephrine into the general circulation and is characterized by hypertension, coldness of the extremities with blanching or mottling of the skin, diaphoresis, accelerated heart rate, dyspnea, and varying degrees of shock. Experimental, clinical, and pathologic evidence is submitted for the authors' explanation of this syndrome.

BERNSTEIN.

Packard, G. B., and Waring, J. J.: Arteriovenous Fistula of the Lung. Arch. Surg. **56**:725 (June), 1948.

The presence of arteriovenous fistula in the lung has been recognized clinically only during the past few years. The steadily increasing number of cases reported suggests that it is much more common than supposed. The authors present a brief review of the literature, the pathologic process, and the symptoms and signs of this condition. The typical syndrome of cyanosis, clubbing of the fingers and toes, and polycythemia, without abnormality of the heart, plus the roentgenographic observations are practically diagnostic. Possible relationship of this condition to hereditary hemorrhagic telangiectasia is indicated, and the incidence of multiple lesions is emphasized.

One of the early cases in which the condition was recognized and treated surgically is reported. This case is the only one, as far as the authors know, in which pulmonary arteriovenous fistula was treated beneficially by single ligation of the pulmonary artery.

Discussion is made of the distinctive features of the pulmonary circulation as compared with the systemic circulation, which may permit some variations in treatment of pulmonary arteriovenous fistula as compared with treatment of fistula in the systemic circulation. Apparently arterial connection between the pulmonary artery and bronchial artery branches is hardly to be compared with the free collateral circulation existing in the systemic circulation.

BECK.

Rasmussen, H., and Moe, T.: Pathogenesis of Left Bundle Branch Block. Brit. Heart J. **10**:141 (July), 1948.

The authors investigated a series of 100 patients with permanent left bundle branch block in an attempt to determine how often left bundle branch block is associated with heart disease causing enlargement of the left ventricle and how often conditions occur that may be supposed to produce a local lesion of the branch.

Seventy-six of the 100 patients studied had left-sided heart disease of aortic or hypertensive nature. Three had myocardial infarction, six were arteriosclerotic, one had a melanocarcinoma, and fourteen presented etiologies of uncertain nature. As determined by x-ray studies or necropsy, forty-five had gross cardiac enlargement, nineteen medium, nineteen slight, and seven no evidence for enlargement. Ten had neither an autopsy nor x-ray study. The average weight of the thirty-one hearts examined at autopsy was 652 grams. One weighed 1,780 grams. This is stated to be the largest heart ever reported.

From this study, it is seen that 72 per cent had disease of the left side of the heart and of those studied by x-ray films or necropsy, sixty-four (71 per cent) had left-sided enlargement of a degree sufficient to explain the bundle branch block. Therefore, left bundle branch block is due five times more often to enlargement of the left heart than to a local lesion of the left branch of the bundle.

On the basis of this study and previous clinical and experimental studies, the authors believe that the electrocardiogram of left ventricular hypertrophy and that of left bundle branch block represent different degrees of retarded conduction of the left heart and the comprehensive term "electrocardiogram of left-sided retardation" is introduced to include all electrocardiographic patterns of retarded conduction of the left heart.

SOLOFF.

Newman, M.: Coarctation of the Aorta; Review of Twenty-Three Service Cases. Brit. Heart J., **10**:150 (July), 1948.

The author presents an analysis of twenty-three patients suffering from coarctation of the aorta, twenty of whom served in the Second World War and three of whom served in the First World War. In this series, coarctation was first diagnosed between the ages of 19 and 37 years. When the condition was first recognized all were well-developed and well-nourished. All had elevated blood pressures in the upper extremities and lower blood pressures in the lower extremities. All had systolic aortic murmurs. Fifteen of the twenty-three persons had abnormal pulsations at the root of the neck, nine had visible collateral pulsations, twenty had an absent or small aortic knuckle, and eleven had erosion of the ribs.

Three of the twenty who served in the Second World War are dead. One died from rupture of the aorta after five years of military service. He had had no previous symptoms. One died on the operating table from cardiac failure during operation for the coarctation. One died of subacute bacterial endocarditis after six years of military service. All the remaining seventeen individuals are living. Of the three who served in the First World War, one died at 68 years of age. One was alive twenty-five years after the initial diagnosis but was receiving treatment for heart failure. The third, 54 years of age, was free of heart failure but was not able to walk far.

It is thus seen that the prognosis of coarctation of the aorta is not too bad if symptoms do not appear until after the age of 20 years, and that severe hypertension may last for many years without causing heart failure and some may live a normal span of life.

SOLOFF.

Harrison, C. V., and Lenox, B.: Heart Block In Osteitis Deformans. Brit. Heart J. **10**:167 (July), 1948.

The authors report the clinical notes and findings at autopsy of two persons who had complete heart block complicating osteitis deformans. In one, a bar of calcification extended the length of the posterior mitral leaflet and had spread to the base of the interventricular septum. In the other, the posterior mitral leaflet was also calcified. All the aortic cusps, the aortic and mitral rings, and the upper posterior two-thirds of the membranous system were the seat of calcification. In a study of the hospital files and the literature, calcification in the heart was found in seventeen of forty-three cases of osteitis deformans (39 per cent) compared to a control series of 8 per cent.

It is concluded that calcification in the heart is five times as common in Paget's disease as in a comparable control series. Heart block is regarded as a complication of this propensity for Paget's disease to develop calcification and progressive fibrosis. The authors state that Paget's

disease affects the heart by tending to produce: (1) high cardiac output; (2) arterial calcification; (3) thoracic deformity; (4) valve calcification; and (5) heart block.

SOLOFF.

Kay, H. B.: Ventricular Complexes in Heart Block. Brit. Heart J. **10**:177 (July), 1948.

To investigate the form of the ventricular complexes present in complete heart block, 100 instances of complete A-V block were studied. In fifty-two the etiology was coronary artery disease; in twenty, congenital; in three, rheumatic fever; in two, diphtheria; in one, syphilis; in one, pneumonia; in two, neurological disease; and in nineteen, the cause was uncertain.

The ventricular complexes were classified into (1) supraventricular pattern, (2) bundle branch block pattern, and (3) varying complexes.

Supraventricular Pattern.—This type was present in forty-seven patients. In nineteen the etiology was congenital; in eleven, coronary artery disease; in four, rheumatic fever or diphtheria; in one, pneumonia; in one, neurologic disease; and in eleven, doubtful. This type occurs when the pacemaker is situated in the main bundle and the branches function normally. This is the rule in congenital heart block. It may also occur as a result of lesions of both bundle branches either because a pacemaker is present in each bundle and both act synchronously or because one pacemaker sends impulses directly through the interventricular septum. This "bilateral missed block" is usually present when there is coronary artery disease, a relatively slow inherent rate, and association of supraventricular complexes with widened ones or occurrence of periods of sinus rhythm with bundle branch block.

Ventricular Complexes of Bundle Branch Block Pattern.—Of forty-seven instances, block of the right bundle branch was present in twenty-nine. Of these, twenty had coronary artery disease; five, myocardial infarction; one, neurologic disease; and three were of doubtful etiology. Block of the left bundle branch was present in six patients. Of these, three had coronary disease; one, congenital heart block; one, rheumatic heart disease; and one was of doubtful etiology. The block was of the concordant type in two; one of the common, and one of the uncommon type.

The pacemaker shifted between the left and right bundles in four patients. Widened ventricular complexes assumed varying patterns in six patients. This may be due to shifting pacemaker, conducted auricular impulses, or ventricular extrasystoles.

Thus, it can be seen that complete heart block with supraventricular complexes is most commonly seen in congenital heart block. The heart rate is faster, Adam-Stokes attacks less common, and the prognosis is better than in complete heart block with widened QRS complexes of the bundle branch block pattern which occurs more commonly in coronary artery disease or other forms of acquired heart disease.

SOLOFF.

Walls, E. W.: The Regenerative Capacity of Mammalian Heart Muscle. Brit. Heart J. **10**:188 (July), 1948.

The opinion most generally held is that hyperplasia of cardiac muscle does not occur. Because of an occasional contradictory statement, the author thought it desirable to study the regenerative power of the myocardium of the rabbit. In adult rabbits the heart was exposed under anesthesia and a severe burn made in the lower third of the left ventricle by the application of the head of a nail, 5.0 mm. in diameter, heated to dull redness. The chest wound was closed and the animals were allowed to survive for periods ranging from three days to three months. No evidence of regeneration of cardiac muscle was observed in the histologic examination of serial sections.

SOLOFF.

Peel, F. A. A.: Tuberculous Pericarditis. Brit. Heart J. **10**:195 (July), 1948.

The author reports eight instances of pericarditis of tuberculous origin. The diagnosis of tuberculosis was confirmed at autopsy in two patients. In two, the diagnosis was made by the finding of an associated active, primary subpleural Ghon lesion. In two, the diagnosis was made by demonstration of associated pleural effusions, in one of which tubercle bacilli were found. In one, the diagnosis was suspected on the basis of bilateral pleural effusion. In the last case, the diagnosis was suspected on the basis of a primary pericardial effusion with cardiac tamponade and fever.

On the basis of his observations, the author believes that the incidence of tuberculous pericarditis has been considerably underestimated. He believes that it arises in the early stage of dissemination of tuberculosis. It is frequently secondary to tuberculous mediastinal lymphadenopathy. Constitutional symptoms such as loss of weight, night sweats, and fever are relatively insignificant. Local symptoms of precordial pain or cough due to pressure may be present. Cardiac tamponade may occur. The striking physical finding is a persistent loud friction rub widely distributed over the precordium. Those instances in which tubercle bacilli cannot be recovered from the pericardial sac have a much better prognosis than those in which the organisms are recovered.

Tuberculous pericarditis may pass through four stages: (1) dry stage; (2) stage of effusion; (3) stage of absorption; and (4) stage of pericardial constriction. Arrest or cure may occur before the stage of effusion or after the stage of absorption. Because the rate of recovery is not known, it is not possible as yet to assess the value of treatment.

SOLOFF.

Peters, J. P.: The Role of Sodium in the Production of Edema. New England J. Med. **239**:353 (Sept. 2), 1948.

This article presents in highly concentrated form a critical analysis of a broad range of investigative data, old and recent, bearing upon the physiologic disorders involved in the development of heart failure and edema. The Starling concept of hydrostatic pressure and colloid osmotic pressure as opposing forces governing the motions of fluid between capillaries and adjacent spaces is reviewed. Evidence is cited supporting the universal application of this hypothesis in the interpretation of edema formation. The author considers measurements purporting to demonstrate the inapplicability of the concept under certain conditions a reflection upon the measurements and not upon the validity of the principle.

Extracellular fluid escapes not only through the capillary wall but also through the lymphatics, which normally carry off the small amount of protein which has passed the capillary membrane or has been delivered from the cells. The stubborn character of the edema of lymphatic obstruction is the result of accumulation of this extracellular protein.

In the liver and portal circulation, the capillary walls are permeable to protein. Since the capillary pressure in this system is very low, fluid transudation could not be accomplished without a high colloid osmotic pressure of the extracellular fluid. There is, therefore, a continuous flow of plasma protein into the extracellular fluid of the portal bed; this returns to the general circulation in the thoracic duct. Since dye methods for plasma volume determination are based upon the distribution of protein-bound dyes, and since an unmeasurable quantity of the dye is constantly being lost from the circulation through the portal extracellular pathway, "it should be evident to reasoning persons that the method can have no value."

The water exchange between cells and extracellular fluid is governed by the osmotic pressure of the latter, which is, in turn, a function of sodium concentration. When the latter is low, the cells swell with water; when it is high, fluid is extracted from the cells.

Of the total glomerular filtrate formed, only about 1 per cent of water and less than 1 per cent of the sodium chloride is ordinarily excreted. The reabsorption of each is in large measure independent of the other. In the proximal tubules, about 80 per cent of the water and a roughly equivalent amount of chloride and of sodium is reabsorbed. Reabsorption of sodium is greater than that of chloride, reducing the sodium chloride ratio 1.3/1.0 to 1.0/1.0. In the loops of Henle, the reabsorption of sodium and chloride is very active, converting the altered filtrate from an isotonic to a hypotonic solution. In the distal convoluted tubule, water reabsorption is predominant, resulting in a hypertonic urine as finally elaborated.

Sodium reabsorption has top priority and is independent of water excretion. Conversely, water excretion is dependent upon the solutes in solution in the distal tubule. Thus, depending upon the amount of sodium remaining in the fluid after passage through the loop of Henle, water reabsorption is impeded. The damaged kidney has impaired sodium reabsorption ability and must, therefore, have impaired water reabsorption function.

Water reabsorption in the distal tubule is under the control of the pituitary antidiuretic prin-

ciple, which is present in large quantities in the urine during dehydration and pathologic edema states. If salt is given with water, the antidiuretic principle cannot prevent diuresis.

Sodium reabsorption is probably controlled by a steroid derived from the adrenal cortex. Cortical extracts stop only abnormal sodium wastes, whereas the synthetic steroid desoxycorticosterone acetate causes sodium retention in the normal subject.

Sodium excretion is powerfully influenced by factors other than the serum concentration. The dehydrated patient may have hypernormal serum sodium concentration, yet excrete very little. This has the physiologically desirable effect of extracting water from cells and permitting excretion of other substances without waste of water. Elaboration of the antidiuretic principle is promoted by increased solutes, especially sodium, in the serum. Hypernatremia also stimulates thirst. It is almost always a sign of dehydration, because if given the opportunity, the animal will dilute the sodium level back to normal by drinking. In diabetes insipidus, deprivation of water results in very high sodium and chloride levels. If the subject is given additional saline, the degree of dehydration is exaggerated.

According to the Starling concept, cardiac edema arises in the following sequence: Increased venous and capillary pressure, transudation, hemoconcentration, retention of salt and water. "This seems a logical sequence, compatible with existing physiologic theory." According to the "forward failure" concept of Warren and Stead, the primary event is retention of salt and water, followed by expansion of plasma volume, increased venous and capillary pressure, and transudation. The premises upon which this concept is based are examined. The demonstration of the plasma volume increase was based on the dye method, which is severely criticized by the author. Those who have carried it to the point of denial of the application of the Starling hypothesis in cardiac edema "deserve no consideration." Landis has shown that back pressure in the capillaries is not delayed until gross sodium retention has occurred. In borderline failure, edema may develop only when the legs are dependent. This edema formation is attended by hemoconcentration. The reasons must be found for blood volume expansion and simultaneous sodium retention if the "forward failure" concept is correct.

In hypoalbuminemia, transudation is followed by diminished blood volume, sodium retention, hypernatremia, and water retention through the activity of the antidiuretic principle. In cardiac edema, capillary pressure elevation may be substituted for hypoalbuminemia as the basis for transudation. Thereafter, the sequences are essentially the same. The administration of mercurial diuretic to the cardiac patient by inhibition of sodium reabsorption, is analogous to the administration of albumin to the nephrotic patient, which, by expansion of blood volume, removes the stimulus to sodium retention.

The author believes that the degree of blood volume expansion in heart failure has been exaggerated. Hepatic engorgement is precisely the condition to give fallacious blood volume determinations by the dye method. As evidence that diuresis in heart failure is regularly accompanied by an increase in plasma volume, the plasma specific gravity studies of Stewart are cited. The most striking diuresis reported by Merrill and Stead was associated with a sharp drop in hematocrit. Loss of circulating fluid is undoubtedly a characteristic of paroxysmal dyspnea and of coronary occlusion. Venesection in these patients is severely condemned. The reported beneficial effects of hypertonic glucose and of blood transfusions are noted.

If the earlier physiologic argument is adhered to, the rationale of salt restriction in cardiac or nephrotic edema is clear. The relative ineffectiveness of water restriction is also explained. Dehydration stimulates sodium retention, which in turn stimulates elaboration of the antidiuretic principle.

If hypernatremia were a primary event in heart failure, mercurial diuresis should be the logical first measure of treatment, as has been advocated. The author has found subnormal sodium levels in some patients in failure; in these, mercurial diuretics are distinctly contraindicated. The suggestion is made that in some patients in heart failure salt administration may be beneficial.

The author concludes that plausibility is no substitute for sound reasoning based upon fundamental scientific principles; that generalization from particulars is dangerous; and that no single organ or system in a complex integrated organism can be considered *in vacuo* apart from the whole.

KAY.

American Heart Association, Inc.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7-2045

GRANTS FOR RESEARCH IN CARDIOVASCULAR DISEASE

Applications for research fellowships and fellowships for established investigators must be filed not later than September 15, 1949.

The majority of the research funds will be devoted to supporting individuals. A limited number of applications for grants-in-aid for research studies in the cardiovascular field and in basic research will be accepted until December 15, 1949.

Fellows desiring research grants-in-aid should submit such applications at the same time as the application for fellowship.

Further information, brochures, and application blanks may be obtained by writing the Medical Director, American Heart Association, 1775 Broadway, New York 19, N. Y.

ADDITIONAL GRANTS-IN-AID

Eleven awards for grants-in-aid, approximating $50,000, were approved by the Board at its June meeting, as follows:

Mary C. Colglazier (University of Kansas); E. Watkins, Jr. (University of Oregon); J. R. Di Palma (Long Island College of Medicine); J. J. Sampson (Harold Brunn Institute for Cardiovascular Research, San Francisco); J. H. Heller (Yale University); H. C. Wiggers (Albany Medical College); H. L. Blumgart (Harvard University); W. C. Sealy (Duke Hospital); W. T. Salter Yale University); C. R. Houck (University of Tennessee); H. C. Bazett (University of Penna.)

AMERICAN FOUNDATION FOR HIGH BLOOD PRESSURE BECOMES SECTION OF SCIENTIFIC COUNCIL

A plan of integration with the American Foundation for High Blood Pressure was approved at the June meeting of the Board of Directors. The Foundation will become one of the constituent Sections of the Scientific Council and will be known as the Council for High Blood Pressure Research.

A preliminary agreement approved by the Boards of both organizations provides for a joint staff study to recommend methods of integrating personnel and operations.

Alva Bradley, of Cleveland, Ohio, Chairman of the Board of Trustees of the American Foundation for High Blood Pressure, was elected a Member of the Board of Directors and of the Executive Committee.

FINANCIAL SUPPORT VOTED

Contributions of $2,500 each were voted by the Board for the International Cardiological Congress, to be held in Paris September 3 to 9, 1950, and for the newly formed Interim Commission on Chronic Illness. An additional $1,000 was voted this Commission by The American Council on Rheumatic Fever.

Regarding the latter group, the following resolution was passed:

> "The Board of Directors of the American Heart Association, being aware of the formation of the Commission on Chronic Illness under the sponsorship of the American Medical Association, American Hospital Association, American Public Health Association, and the American Public Welfare Association, and recognizing the mutuality of interests and the common objectives of the American Heart Association, and the Commission as regards the problem of chronic illness,
>
> "HEREBY RESOLVES to contribute the sum of $2,500 to help meet the budget of the Commission for the year July 1st, 1949-June 30, 1950, as evidence of its desire to endorse, support, and participate in the program of the Commission on Chronic Illness.
>
> "IT FURTHER RESOLVES, that the President of the American Heart Association be authorized to address a letter to local heart associations and the various sections and councils of the American Heart Association urging them to cooperate in all appropriate ways with the work of the Commission, and specifically presenting to them the opportunity for contributing financially to the Commission in the name of the American Heart Association, its councils, sections, and local affiliates."